Dissertation on

hs-CRP AS A MARKER FOR DIASTOLIC DYSFUNCTION IN PATIENTS WITH CARDIOVASCULAR RISK FACTORS

Submitted in partial fulfillment of Requirements for

M.D.DEGREE BRANCH I

GENERAL MEDICINE of

THE TAMILNADU DR.M.G.R. MEDICAL

UNIVERSITY CHENNAI

INSTITUTE OF INTERNAL MEDICINE

MADRAS MEDICAL COLLEGE

CHENNAI–600003

APRIL – 2014

BONAFIDE CERTIFICATE

This is to certify that this dissertation entitled **"hs-CRP as a marker for diastolic dysfunction in patients with cardiovascular risk factors**" submitted by **Dr.V.C.POORNACHANDRAN** appearing for M.D. Branch I General Medicine Degree examination in April 2014 is a bonafide record of work done by him under my direct guidance and supervision in partial fulfillment of regulations of the TamilNadu Dr. M.G.R.Medical University, Chennai. I forward this to the TamilNadu Dr.M.G.R.Medical University,Chennai,Tamil Nadu,India

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DECLARATION

I solemnly declare that the dissertation entitled **"hs-CRP as a marker for diastolic dysfunction in patients with cardiovascular risk factors"** was done by me at Madras Medical College & Rajiv Gandhi Govt. General Hospital, Chennai during 2013 under the guidance and supervision of **Prof. K.SIVASUBRAMANIAN.M.D.** This dissertation is submitted to the Tamilnadu Dr.M.G.R. Medical University towards the partial fulfillment of requirements for the award of M.D. Degree (Branch -I) in General Medicine.

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ACKNOWLEDGEMENT

I would like to thank our respected Dean, Madras Medical College,

Prof Dr.V.KANAGASABAI,M.D.,M.B.A., for his kind permission to use the hospital resources for this study.

I would like to express my sincere gratitude to my beloved
Chief, Professor and Director, Institute of Internal Medicine
Prof. K SIVASUBRAMANIUM ,M.D., for his guidance and encouragement.

I am extremely thankful to Assistant Professors of Medicine of our unit
Dr.Aparna and **Dr.Sharmila** for their co-operation and guidance.

I thank the DEPARTMENT OF CARDIOLOGY for their extreme cooperation extended to me without whom the study would not have been possible. I especially like to express my thanks to **Prof.V.E. DHANDAPANI, M.D.,D.M.,** Professor & HOD, department of Cardiology for his cooperation and guidance.

I sincerely thank my family, my colleagues and my fellow postgraduates for their help and support. Last but not the least, I thank all my patients for their kind participation in this study.

Above all I thank Almighty for His immense blessings and guidance.

ABBREVIATIONS

ACE- Angiotension converting enzyme

BMI- Body mass index

CRP- C-reactive protein

DD- Diastolic dysfunction

DD I- Diastolic dysfunction Grade I

DD II- Diastolic dysfunction Grade II

DHF – Diastolic heart failure

DL- Dyslipidemia

DM- Diabetes mellitus

DT- Decelaration time

ECG- Electrocardiogram

ECM- Extra cellular matrix

HF- Heart failure

Hs-CRP- High sensitivity c-reactive protein

HT- Hypertension

IVRT- Isovolumic relaxation time

LV- Left ventricle

LVH- Left ventricular hypertrophy

RAAS- Renin angiotensin activating system

SHF- Systolic heart failure

SR- Sarcoplasmic reticulum

TPFR- Time to peak filling rate

ABSTRACT

BACKGROUND: Diastolic dysfunction (DD) is present in more than one third of patients with heart failure. Different mechanisms have been postulated for the pathogenesis of DD. Among them, inflammatory hypothesis is well documented. High sensitivity- c reactive protein (hs-CRP) is a well known biomarker of inflammation. Hence, we analyzed the relationship between serum hs-CRP levels and diastolic dysfunction in patients with cardiovascular risk factors such as hypertension, diabetes mellitus and dyslipidemia.

METHODS: We randomly selected 100 outpatients with cardiovascular factors who were asymptomatic and taking medications. They were divided into six groups depending upon the no of risk factors they had. We measured their serum hs-CRP levels by immunoturbidometry, and estimated their left ventricular diastolic function using echocardiography. Statistical analysis was done to find the association between the two variables.

RESULTS: Among the 100 patients: males were 56, females 44, the mean age was 52±9, the mean BMI was 30.5±3.18, 20% were hypertensives, 20% had diabetes mellitus, 22% had both diabetes and hypertension,10% had hypertension and dysplipidemia, 14% had diabetes and dyslipidemia, and 14% had all three risk factors. Diastolic dysfunction was present in 62% of the patients of which 66.13% had Grade I diastolic dysfunction and 33.87% had Grade II diastolic dysfunction. Statistical analysis showed significant association between age and DD ($p<0.001$) as well as between BMI and DD ($p<0.001$). There was a strong relationship between hs-CRP levels and DD ($p=0.001$)

CONCLUSION: Elevated hs-CRP level is independently associated with diastolic dysfunction in asymptomatic patients with cardiovascular risk factors.

KEYWORDS: Diastolic dysfunction, hs-CRP, cardiovascular risk factors.

INTRODUCTION

Heart failure is a clinical syndrome in which an abnormal cardiac function causes failure of the heart to pump blood that is needed to maintain the metabolic requirements of various tissues. This could be due to either a contraction or relaxation abnormality, former is called as systolic failure and the latter is termed diastolic failure.

Diastolic dysfunction occurs in approximately 40-50% [1] of people with heart failure. Various mechanisms are involved in the pathogenesis of diastolic dysfunction. Inflammatory fibrosis is a major factor implicated in diastolic dysfunction.

Traditional cardiovascular risk factors such as diabetes mellitus, hypertension are pro-inflammatory states that could cause myocardial stiffening and result in diastolic dysfunction.

C - reactive protein (CRP) is an acute phase protein produced in the liver in response to inflammation in the body. It has been used to predict cardiovascular risk in the general population.

Recent studies[2, 3] have shown that there is definite correlation between diastolic dysfunction and hs-CRP levels in blood in patients with cardiovascular risk factors.

Ridker et al. 2000 and Olsen et al. 2008 showed that hs-CRP could be used to predict cardiovascular events in the general population.

Torwezki et al. 1998 and Zwaka et al. 2001 found that hs-CRP could play a role in the pathogenesis of atherosclerosis.

deFillipi et al. 2003. and conen et al.2006 gave us some data regarding the risk of major adverse cardiac events in patients with cardiovascular risk factors.

Rajaram V et al 2011 and Masugata et al. 2011 have reported a significant association between hs-CRP levels and diastolic dysfunction in patients with cardiovascular risk factors.

REVIEW OF LITERATURE

Heart failure (HF) occurs when the heart is not capable to pump adequate amount of blood to meet the metabolic demands of various tissues.

Historical Aspects:

Manuscripts about heart failure can be found in the ancient medical literature in Egypt, Greece, and India. Foxglove was used by the Romans to treat heart failure.

William Harvey explained about the circulation which helped to gain new insights about heart failure in 1926. The advent of x-rays and electrocardiography in 1890s significantly improved the investigation of heart failure. Newer modalities like echocardiography, cardiac catheterization, and nuclear medicine have widened the diagnostic options in heart failure and helped in improving patient care.

Phlebotomies and leeches were used in the very early period. William Withering described about the uses of digitalis in 1785. Southey's tubes were used to drain the fluid from the peripheries in the 19th and 20th centuries. In the 1950s thiazide diuretics were started to be used in heart failure[4]. Vasodilators like angiotension converting enzyme inhibitors were introduced in 1970s[5]. CONSENSUS-I study report published in 1987 proved without doubt the survival benefits of enalapril in patients having severe heart failure[6].

EPIDEMIOLOGY OF HEART FAILURE

Heart failure has become a significant public health problem and has reached epidemic proportions. It is causing significant morbidity and mortality and is draining a major chunk of the health care expenses.

More and more patients are presenting with diastolic heart failure for which definitive therapy is still lacking. Hospital admission and readmissions have increased over a period of time.

PREVALENCE

The prevalence of heart failure is around 1–2% in the US and Europe[7] .

As per American Heart Association (AHA) 2013 update, there were 5.1 million people with heart failure in the US in 2006 and 23 million people with heart failure worldwide[8].

Prevalence of heart failure increases with age. Framingham Heart Study showed a prevalence of HF in men of 8 per 1000 at age 50 to 59 years, which increased to 66 per 1000 at ages 80 to 89 years, same trend was noted in women. The prevalence in African-Americans was found to be 25 percent more than in whites[9].

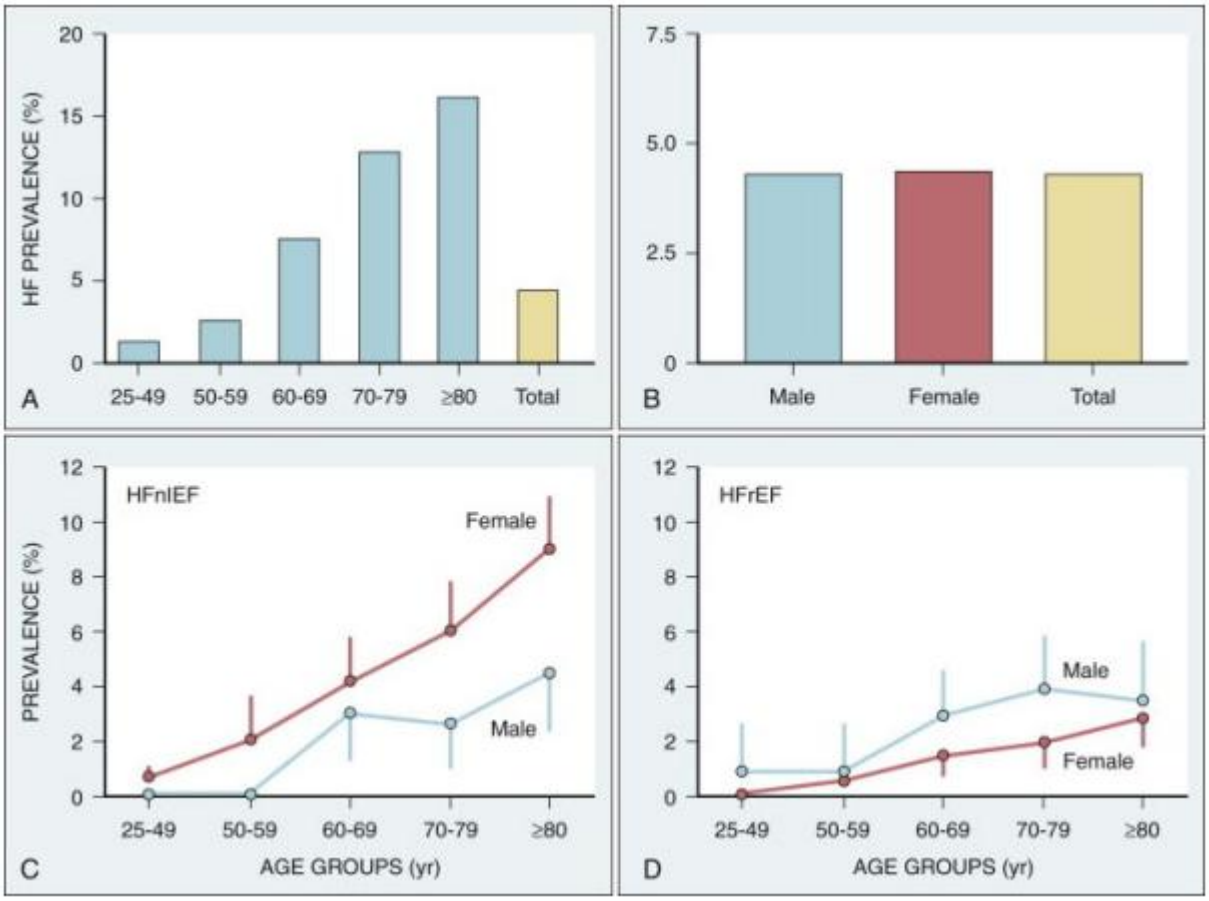

Fig1.Prevalence of Heart Failure[10]

INCIDENCE:

Incidence of heart failure is up to 5-10 per thousand per year[11]

Nearly half a million people newly develop heart failure annually in the United States each year[12].

The incidence of heart failure is equal among men and women, and African-Americans have 1.5 times more chance of developing heart failure than whites[13].

One in 9 deaths in 2009 was contributed by heart failure. About 50% of people who develop heart failure die within 5 years of diagnosis[14].

Indian Scenario:

Accurate estimates of the incidence and prevalence of heart failure is lacking in India, however a conservative estimate of the prevalence of heart failure due to ischemic heart disease, obesity, diabetes, hypertension and rheumatic heart disease ranges from 1.3 to 4.6 million, with an annual incidence of 0.45-1.8 million[15].

Lifetime risk:

According to Framingham Heart study, in male and female above 40, the life time risk of developing heart failure is about 20%.Without preceding MI, the chance of developing heart failure, at age 40,was 11% for men and 16% for women.

Mortality:

Heart failure causes nearly 287,000 deaths a year. Sudden death is six to nine times more common in patients with CHF than the general population. Deaths from heart failure have decreased by approximately 12 percent per decade for both male and female over the past fifty years.

This can be attributed to current therapies for cardiac disorders, such as myocardial infarction (MI), valvular heart disease, and arrhythmias, which are increasing the longevity[16].

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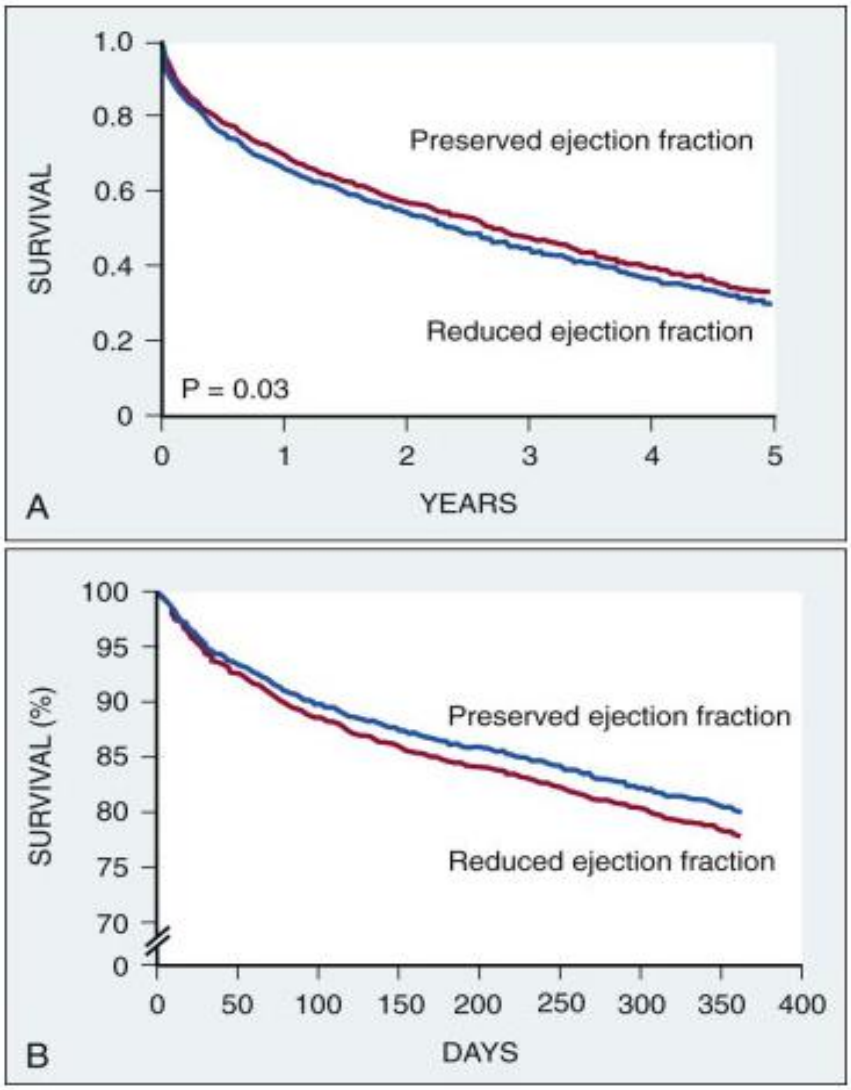


COMPARISON OF SURVIVAL IN SYSTOLIC AND DIASTOLIC FAILURE

EPIDEMIOLOGY OF DIASTOLIC HEART FAILURE (DHF)

Data from various epidemiologic studies suggest that prevalence of diastolic heart failure to be around 40-50%[17]. The prevalence of diastolic dysfunction increases rapidly with age, this phenomenon is more prominent in female than in male.

Mortality:

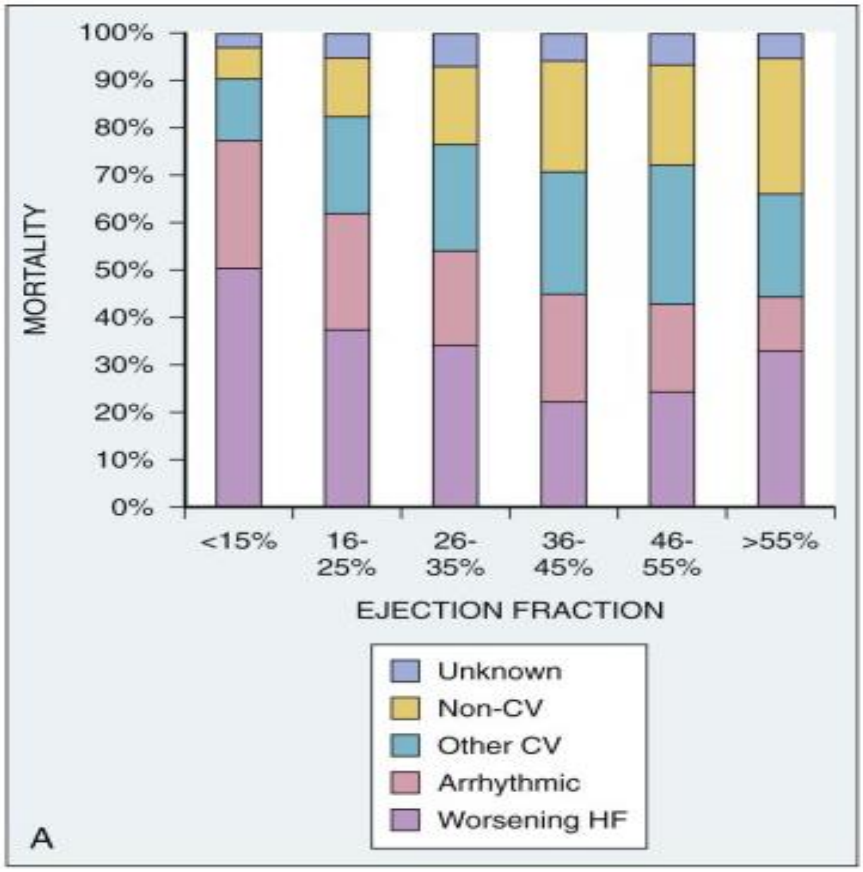
The prognosis of patients with diastolic heart failure is marginally better than patients with systolic failure [18]. The annual mortality rate for patients with diastolic heart failure approximates 5% to 8%[19].

Morbidity:

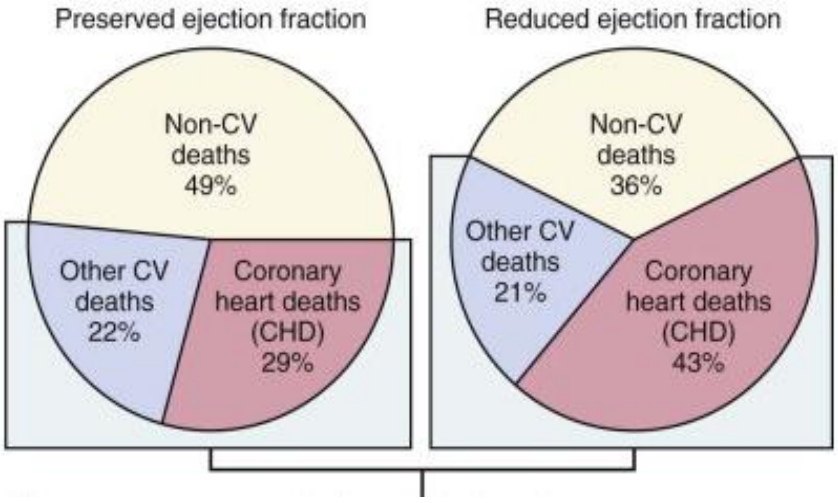
Most of the studies that have compared the morbidity rates in SHF and DHF have reported more or less similar outcomes[20] . The factors that were considered were hospital admission rates, six minute walk distance and Minnesota living with heart failure questionnaire.

Morbidity from diastolic heart failure is ever increasing, causing frequent outpatient treatment, hospital admissions, and the expenditure of significant healthcare resources.

Half of the patients with diastolic heart failure get readmitted within a year. This morbidity rate is similar to patients with systolic heart failure.



Cause of death in patients with HFnlEF.



Comparison of cause of death in diastolic and systolic failure

HEART FAILURE: TYPES

Heart failure can be divided into two types based on the mechanisms involved namely:

- Heart failure with reduced ejection fraction (systolic heart failure)
- Heart failure with preserved ejection fraction(diastolic heart failure)

SYSTOLIC HEART FAILURE

CAUSES[21]:

Coronary artery disease

- Myocardial infarction
- Myocardial ischemia

Chronic pressure overload

- Obstructive valvular disease
- Hypertension

Chronic volume overload

- Regurgitant valvular lesions
- Left to right shunts
- Extracardiac shunts

Non ischemic cardiomyopathy

- Familial and inherited disorders
- Toxic and drug induced
- Metabolic
- Viral myocarditis
- Chagas disease

In developed countries coronary artery disease is the leading cause of systolic heart failure, it contributes to 60% to 75% of the cases of heart failure[22].
While in developing countries valvular heart disease is a major contributing factor.
Hypertension, diabetes mellitus and coronary artery disease are rapidly emerging as significant factors causing heart failure in developing nations.
In about 20-30% cases of heart failure the exact etiology could not be found out. They are referred to as non-ischemic, dilated and idiopathic cardiomyopathy.
Many cardiomyopathies are increasingly being attributed to genetic defects involving the cytoskeletal proteins namely desmin, cardiac myosin,laminin and vinculin. Familial cardiomyopathies are inherited in a autosomal dominant fashion. Muscular dystrophies like Duchene's, Becker's and limb girdle are associated with dilated cardiomyopathies.

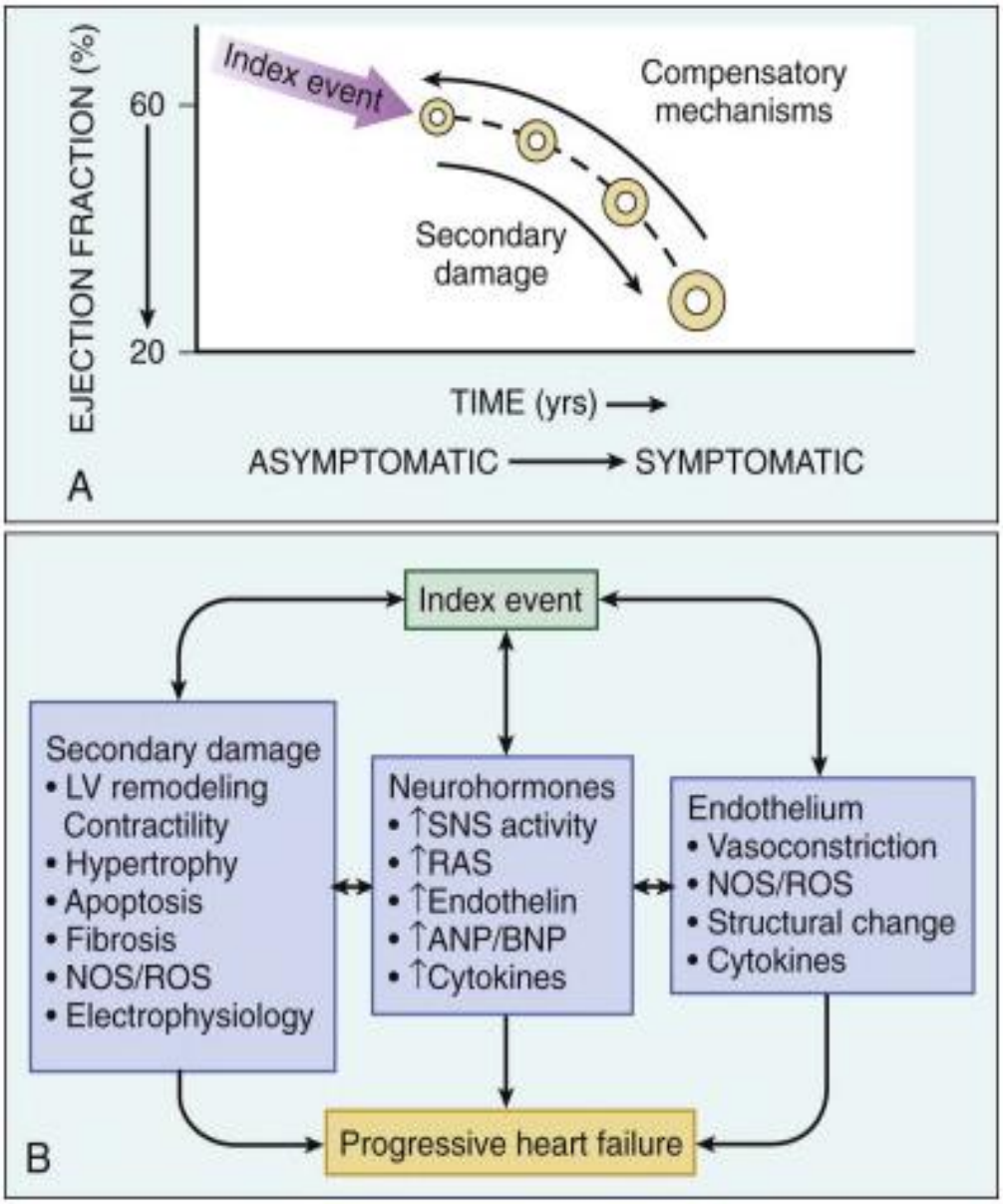
PATHOGENESIS OF SYSTOLIC FAILURE

HF may be viewed as a progressive disorder that is initiated after an index event either damages the cardiac muscle, with a resultant loss of functioning cardiac myocytes or alternatively disrupts the ability of the myocardium to generate force, thereby preventing the heart from contracting normally.

This index event may have an abrupt onset, as in the case of myocardial infarction, or it may have gradual or insidious onset, as in the case of hemodynamic pressure or volume overload; or it may be hereditary, as in the case of many genetic cardiomyopathies.

Regardless of the inciting event, the feature common to each of these index events is that they all in some manner produce a decline in the pumping capacity of the heart.

In majority of cases the patient remains asymptomatic for a long period of time after the initial decrease in pumping capacity of the heart. They present mostly when some acute event precipitates an acute decompensated heart failure[23].



Pathogenesis of heart failure with a depressed ejection fraction[24]

Systolic Heart Failure: Basic Mechanisms

LV remodeling occurs as a reaction to a series of complex events that happen at the cellular and molecular levels

Overview of Left Ventricular Remodeling
Alterations in Myocyte Biology
Excitation-contraction coupling
Myosin heavy chain (fetal) gene expression
Adrenergic desensitization
Hypertrophy
Myocytolysis
Cytoskeletal proteins
Myocardial Changes
Myocyte loss
Necrosis
Apoptosis
Autophagy
Alterations in extracellular matrix
Matrix degradation
Myocardial fibrosis

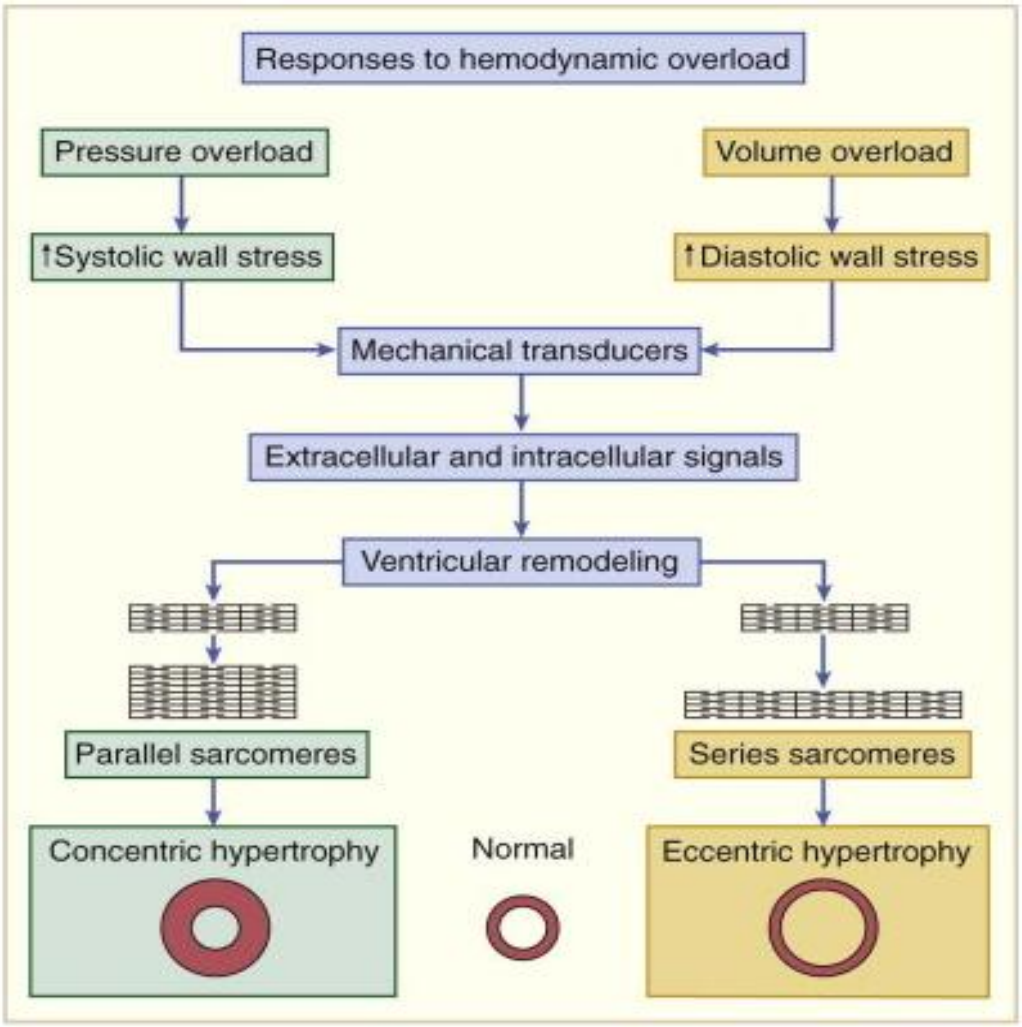
Alterations in Left Ventricular Chamber Geometry
Left ventricular (LV) dilation
Increased LV sphericity
LV wall thinning
Mitral valve incompetence

Sustained neurohormonal activation and mechanical overload result in transcriptional and posttranscriptional changes in the genes and proteins that regulate excitation-contraction coupling and cross-bridge.

The changes that regulate excitation-contraction include decreased function of sarcoplasmic reticulum Ca^{2+} adenosine triphosphatase (SERCA2A), resulting in decreased calcium uptake into the sarcoplamsic reticulum (SR), and hyperphosphorylation of the ryanodine receptor, leading to calcium leakage from the SR. The changes that occur in the cross-bridges include decreased expression of -myosin heavy chain and increased expression of -myosin heavy chain, myocytolysis, and disruption of the cytoskeletal links between the sarcomeres and the extracellular matrix. Collectively, these changes impair the ability of the cardiac myocyte to contract and contribute to the depressed LV systolic function observed in patients with HF. Eventually leading to the

progression of heart failure by virtue of the harmful effects on the heart and circulation.

Changes in Cardiac myocyte in response to hemodynamic load[25]

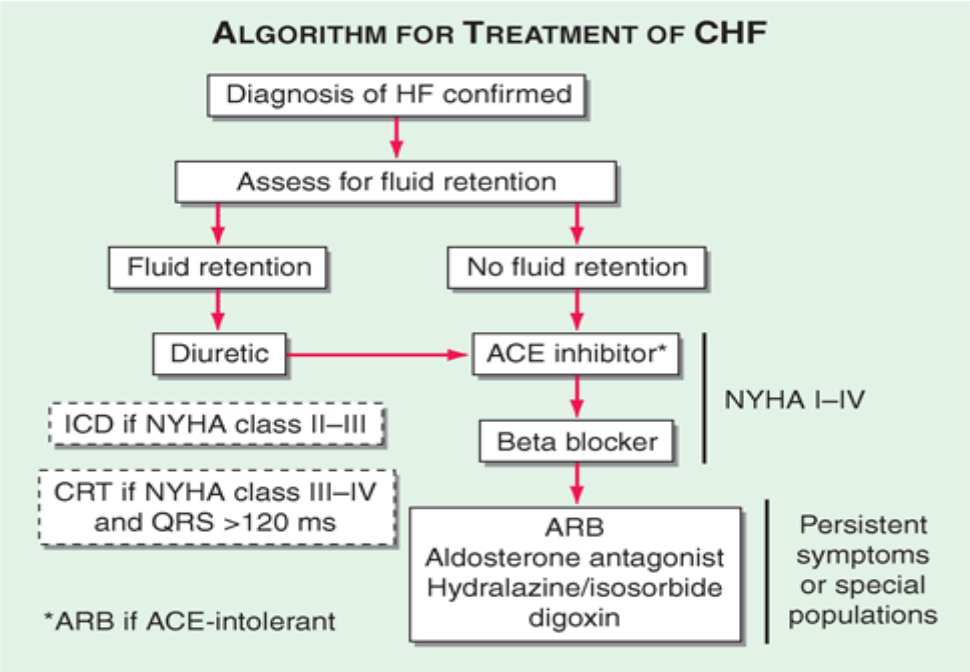


Treatment of chronic heart failure patients with a depressed ejection fraction

After the clinical diagnosis of HF is made, it is important to treat the patient's fluid retention before starting an ACE inhibitor (or an ARB if the patient is ACE-intolerant).

Beta blockers should be started after the fluid retention has been treated and/or the ACE inhibitor has been uptitrated. If the patient remains symptomatic, an ARB, an aldosterone antagonist, or digoxin can be added as "triple therapy."

The fixed-dose combination of hydralazine/isosorbide dinitrate should be added to an ACE inhibitor and a beta blocker in African-American patients with NYHA class II–IV HF. Device therapy should be considered in addition to pharmacologic therapy in appropriate patients



DIASTOLIC DYSFUNCTION (DD):

Diastolic dysfunction is a term used to denote a problem in the mechanical properties of the ventricle such as relaxation, distensibility, and filling.

DIASTOLIC HEART FAILURE (DHF)

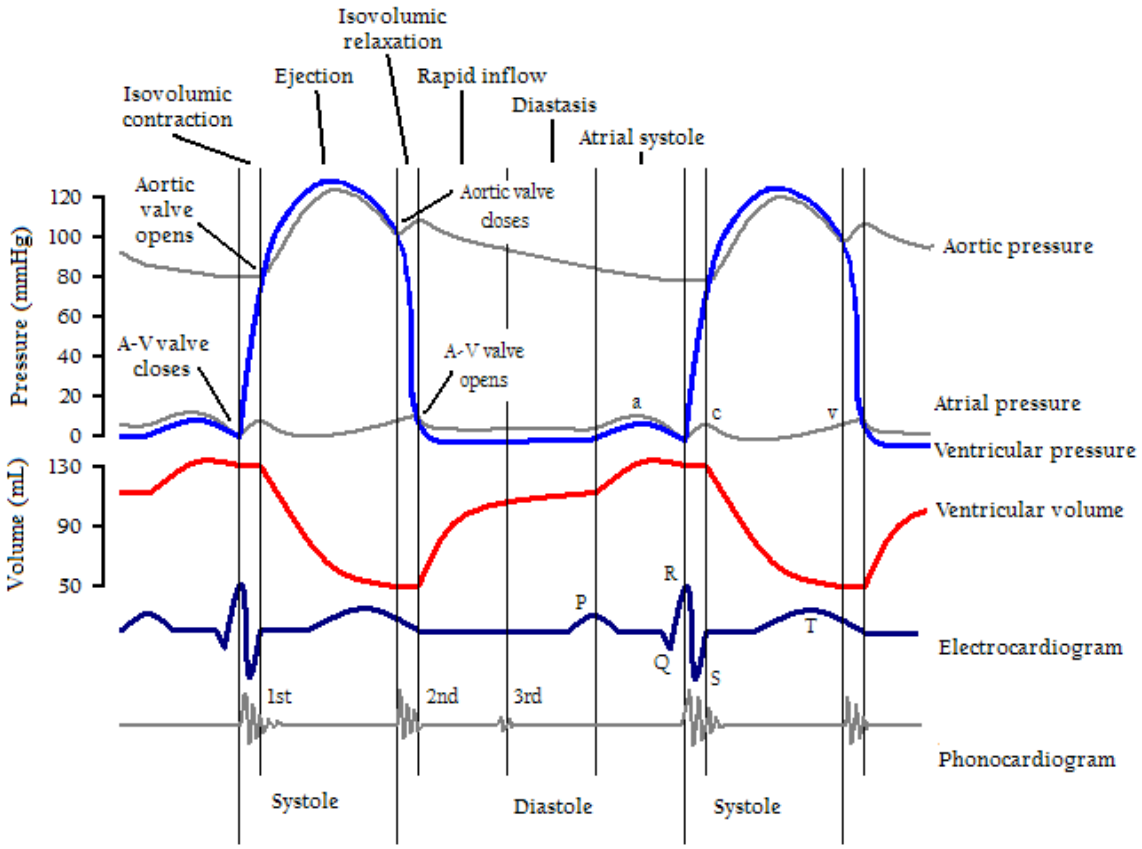
DHF indicates the signs and symptoms of clinical HF in a patient with a normal EF and LV diastolic dysfunction.

Diastolic heart failure occurs when there is decrease in the performance of the ventricles during diastole. During diastole heart relaxes and filled with blood returned through superior and inferior vena cava to right atrium and through the pulmonary veins to the left atrium.

Physiology of diastole:

During diastole, the ventricular pressure drops from the peak attained at the end of systole. When this pressure decreases below the atrial pressure, atrio-ventricular valves open and the blood passes from the atria into the ventricles. First, ventricles are filled by a pressure difference but at the end, atria contract and force more blood to pass into ventricles. Atrial contraction contributes to 20% of the total filling blood volume[26]. Normal left ventricular filling is necessary to maintain an adequate cardiac output. Left ventricular filling is

governed by ventricular relaxation and compliance, atrio-ventricular gradient, atrial contraction, mitral valve area and end-systolic volume.



PHASES OF CARDIAC CYCLE

Diastole has four phases:

- Isovolumetric relaxation
- Rapid filling phase
- Diastasis

- Atrial contraction

Isovolumetric relaxation:

It is the part of the cardiac cycle placed between aortic valve closure and mitral opening, during which the ventricular muscle decreases its tension without lengthening so that ventricular volume remains unaltered. Left ventricular pressure decreases below the pressure in the aortic root, which closes the aortic valve. When the LV Pressure becomes less than the left atrial pressure, the mitral valve opens, and rapid filling begins.

Rapid filling phase:

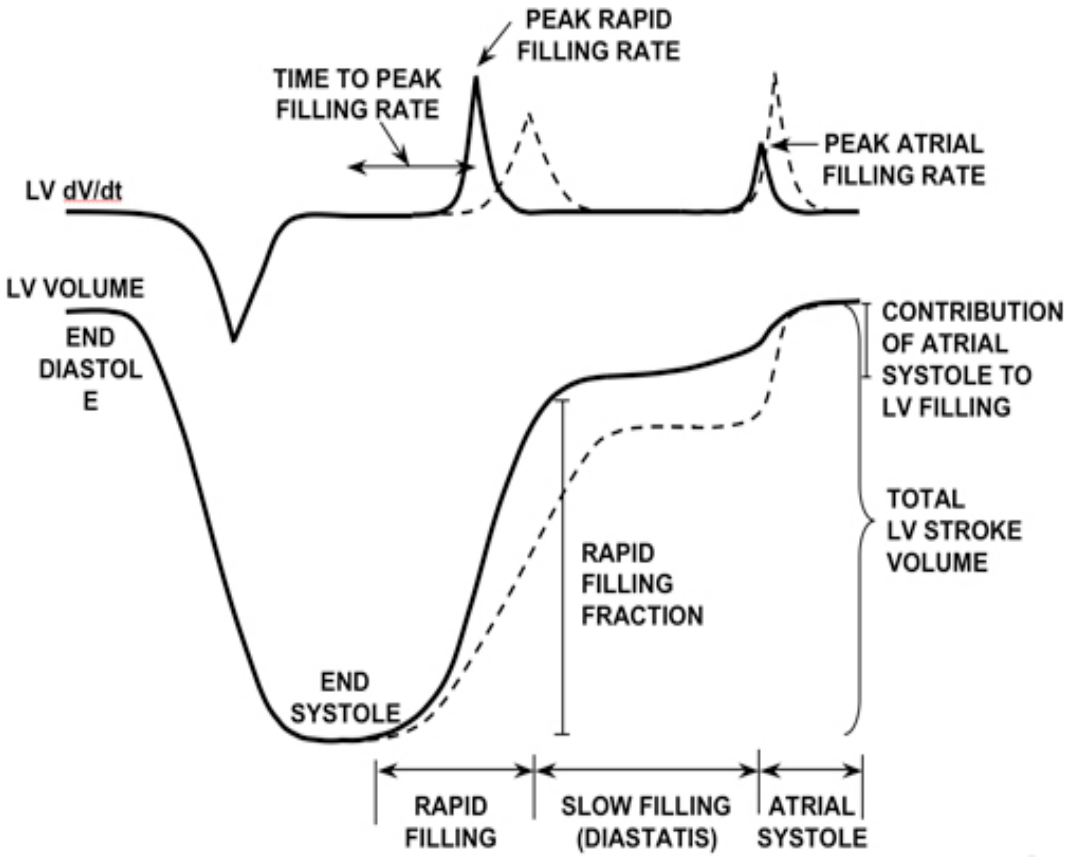
When left ventricular pressure becomes less than left atrial pressure the mitral valve opens. Rapid filling of the left ventricles occurs which is governed by the atrioventricular pressure gradient and the impedance of the mitral valve

Diastasis:

Diastasis is the middle stage of diastole during which the initial passive filling of the ventricles has slowed down, due to decrease in the atrio-ventricular pressure gradient. It is represented by the H-wave in the jugular venous pulse tracing.

Atrial contraction:

During this phase the atrium contracts and forces the blood into left ventricle. This phase is influenced by left atrial function. This phase is responsible for the production of S4. It is present in when the ventricle compliance is reduced as seen in ventricular hypertrophy and in old age.



DIASTOLIC DYSFUNCTION –PATHOPHYSIOLOGY

Diastolic dysfunction occurs when there is change in the mechanical properties of the left ventricle such as myocardial relaxation and passive ventricular filling. It is caused by the following mechanisms.

Slow/incomplete myocardial relaxation:

When the left ventricle is hypertrophied, the decrease in the rate of pressure in the left ventricle during diastole is delayed, ultimately leading to impaired relaxation. This is the cause of diastolic dysfunction in left ventricular hypertrophy.

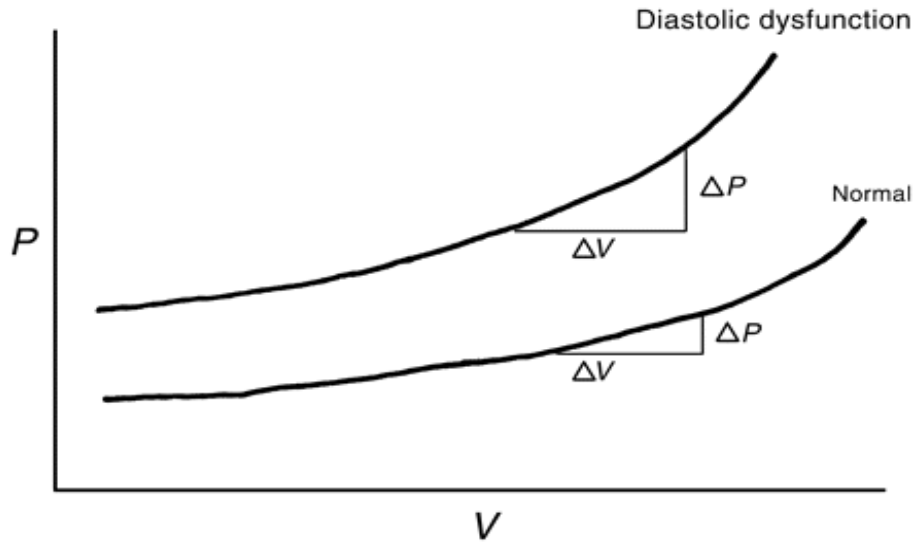
Decreased ventricular peak filling rate:

The filling rate depends on the pressure gradient between the left ventricle and atrium, and the ability of the left ventricle to generate a negative pressure to draw blood into it. If either is affected then diastolic dysfunction can occur.

Structural changes:

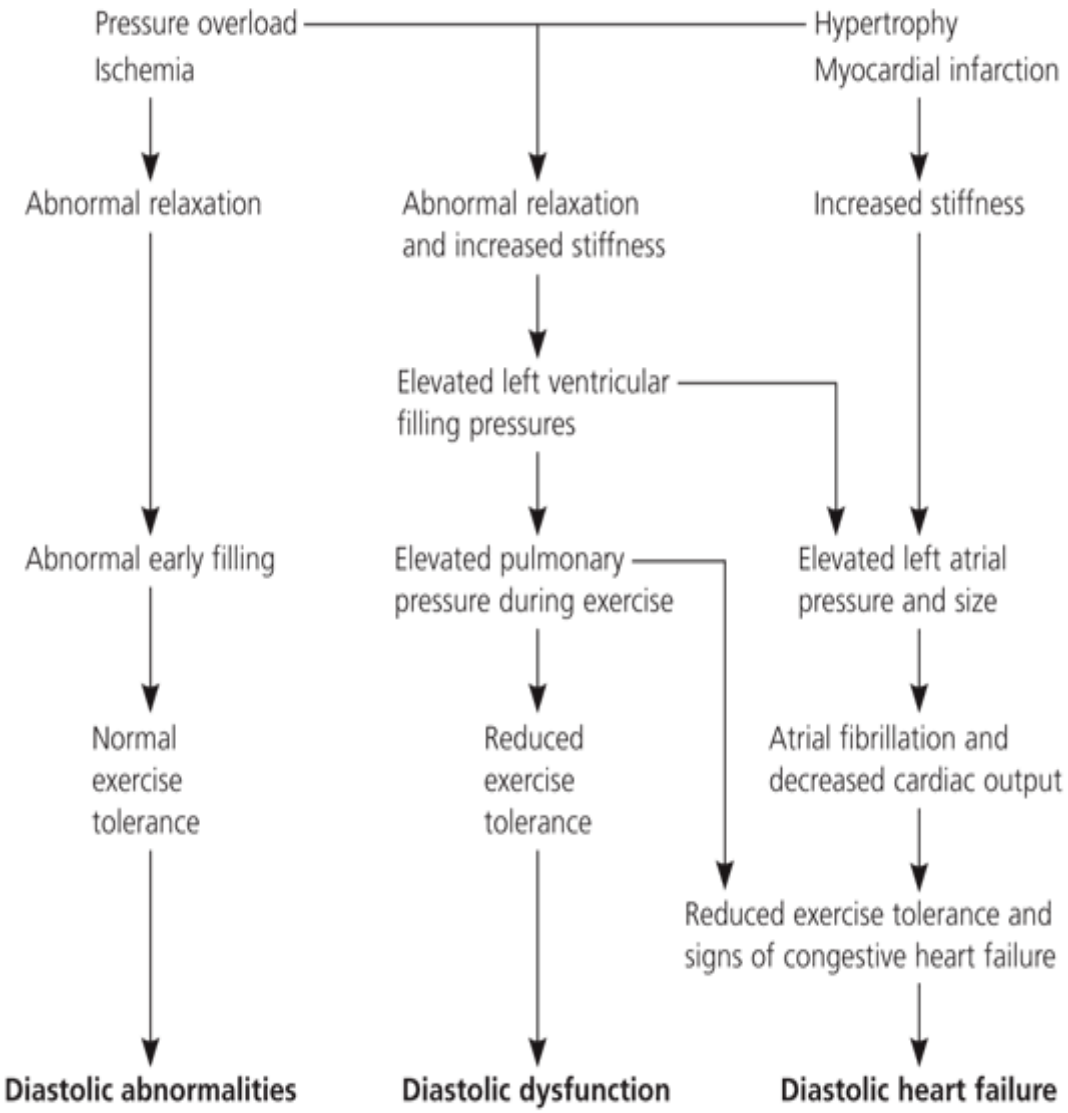
Changes happening in the extracellular matrix causes loss of elasticity of the left ventricle leading to stiffness, neurohumoral mechanisms can be attributed to these events.

Extramyocardial causes: Pericardial diseases can elevate the LV pressure and impair LV filling. Eventually these mechanisms will cause a steeper rise in LV end-diastolic pressure (LVEDP) at any given LV end-diastolic volume (LVEDV) than what occurs in a normal left ventricle[27]



(Pressure–volume curve of LV in diastole in DD, the curve clearly depicts a increased change in pressure for a given volume occurring in DD.)

Pathophysiology of Diastolic Dysfunction: Algorithm[28]



DIASTOLIC DYSFUNCTION: MECHANISMS

Mechanisms that cause diastolic dysfunction can be divided into two types namely myocardial and extramyocardial.

Extramyocardial:

- Hemodynamic load: early diastolic load, after load
- Heterogeneity
- Pericardium

Myocardial:

- Cardiomyocyte
    - Calcium homeostasis alteration
    - Myofilament modifications
    - Energetics
    - Cytoskeleton changes
- Extracellular matrix
- Neurohumoral activation

Cardiomyocyte:

Changes in the calcium homeostasis

- Abnormalities in the sodium calcium exchanger and calcium pump causing expulsion of calcium from the cytosol.

- Decrease in sarcoplasmic reticulum(SR) calcium ATPase causing problems in SR ca2+ .
- Changes in phospholamban, calmodulin, and calsequestrin which modify SR Ca2+ ATPase.

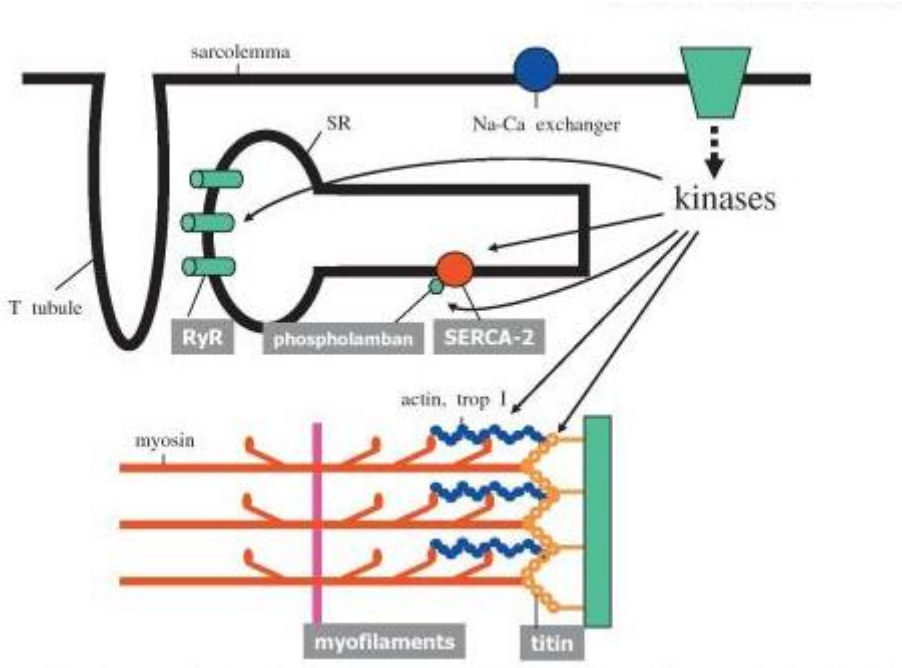
These above changes increase the cytosolic calcium concentration during diastole and slow down the decline of calcium in diastole, resulting in abnormal relaxation and passive stiffness[29].

Myofilaments:

Myofilament consists of thick-filament myosin and thin-filament actin proteins. Regulatory proteins such as tropomyosin, troponin(Tn), T,C and I are bound to actin. ATP hydrolysis is needed for myosin separation from actin during relaxation and also for calcium detachment from Tn-C, and sequestration of calcium in SR.

For normal diastolic function the products of ATP hydrolysis such as ADP and Pi should be less than ATP, if the ratio is altered then diastolic dysfunction occurs[30].

Cardiomyocte cytoskeleton contains microtubules, desmin, actin, titin, nebulin, alpha-actinin, myomesin. Cytoskeletal alterations have shown to cause diastolic dysfunction. Especially titin isotypes modifications have been reported to cause impaired relaxation and viscoelastic stiffness[31].



Myofilament Modifications: Abnormalities of calcium reuptake proteins

Extracellular matrix:

Myocardial ECM contains

- Fibrillar proteins: collagen type I-III and elastin
- proteoglycans
- basement proteins-, laminin, collagen type IV and fibronectin.
- Disease processes that causes diastolic dysfunction cause alterations in the amount, distribution, geometry, degree of crosslinking, ratio of typeI to typeII collagen[32].

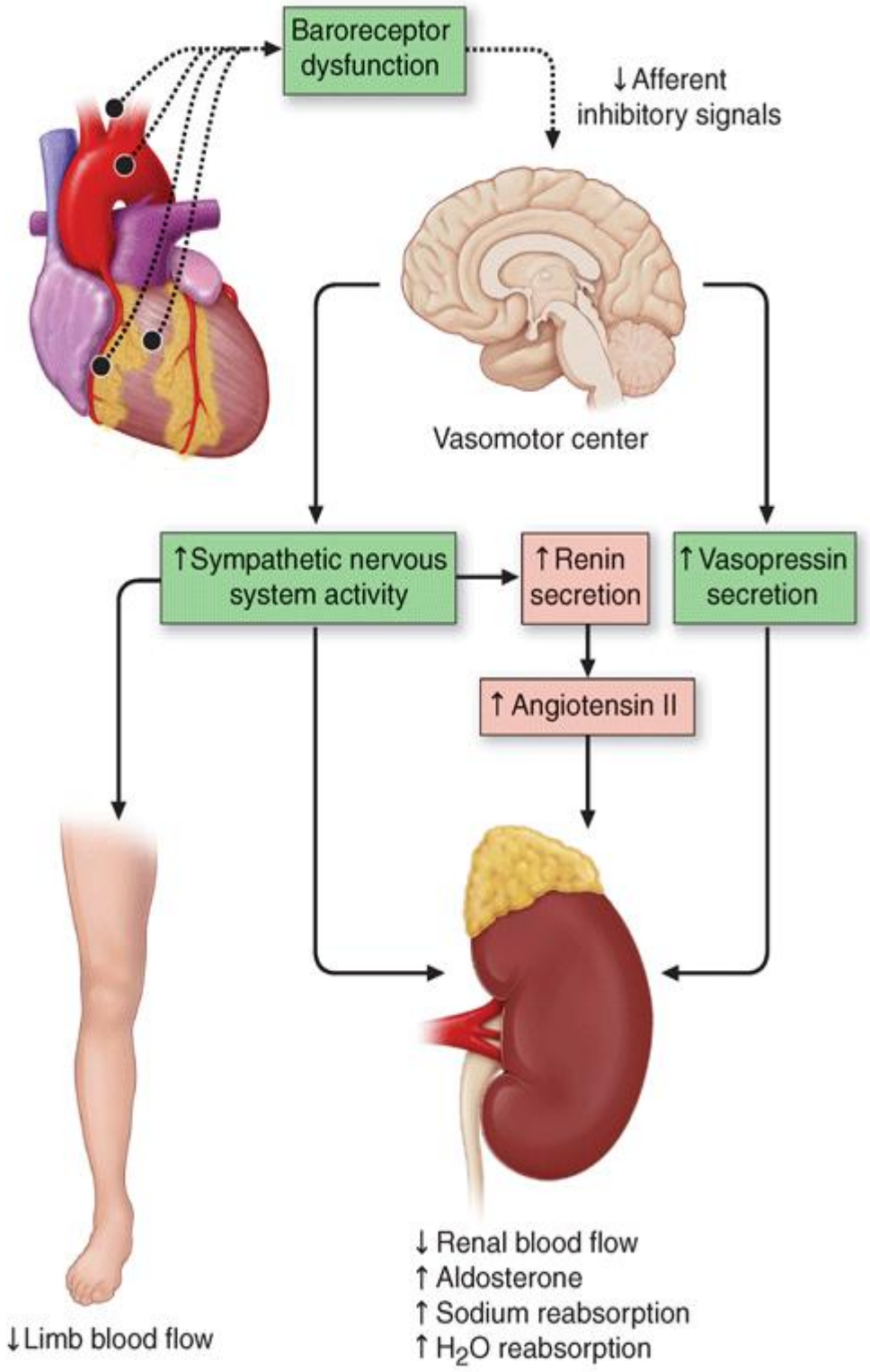
Treatments that normalize diastolic function also correct the above mentioned changes.

Neurohumoral and cardiac endothelial activation:

Neurohumoral activation on the long run can cause diastolic dysfunction. Chronic activation of RAAS increases the ECM fibrillar collagen and causes stiffness. Inhibition of RAAS decreases the fibrillar collagen and eases the myocardial stiffness[33]. Not only chronic but also acute activation or inhibition of the neurohumoral and cardiac endothelial units can alter the diastolic properties of the left ventricle.

Treatment with ACE inhibitor and direct NO donor decreases the left ventricular pressure and shifts the pressure vs volume curve to the right ultimately decreasing the stiffness.

There is a periodic release of nitric oxide mainly subendocardially which happens at the moment of relaxation and filling. This also plays an important factor in the duration of diastolic relaxation. Newer drug like the indirect endothelin-dependent nitric oxide donors target this pathway.



Activation of neurohormonal systems in heart failure

AETIOLOGY OF DIASTOLIC DYSFUNCTION

Diastolic Dysfunction: Causes

Common causes:

- Cardiac ischemia
- Hypertension
- Aging
- Obesity
- Aortic stenosis
- Diabetes mellitus
- Renal dysfunction
- Obstructive sleep apnea

Rare causes:

- Hypertrophic cardiomyopathy
- Amyloidosis
- Sarcoidosis
- Hypereosinophilic syndrome
- Glycogen storage diseases
- Hemochromatosis
- Constrictive pericarditis

- Pericardial effusion

Aging:

Diastolic dysfunction steadily declines with age, even in the absence of cardiovascular diseases.

Structural cardiac changes with aging such as increased cardiomyocyte size, increased apoptosis, and focal collagen deposition may contribute to diastolic dysfunction with normal aging[34]

Gender:

Female sex is prone for developing DHF. Prevalence of diastolic dysfunction increases as age increases in women for not clearly attributable reasons.

Vascular and LV systolic and diastolic stiffness is more in women than men, and these factors increase more steeply in females[35].

Obesity:

Obesity is more common in DHF than systolic failure. Obese persons are more prone to develop diastolic dysfunction[36].

Enhanced adiposity is a source of many biologically active peptide and nonpeptide mediators which in turn lead to chronic inflammation. Increased

BMI is a breeding ground for cardiovascular risk factors such as hypertension, diabetes mellitus, which in turn lead to diastolic dysfunction.

Hypertension:

Hypertension is the most common risk factor for development of DHF.

Long standing hypertension causes left ventricular remodeling and functional changes. Hypertension leads to LVH, augments ventricular stiffness, reduces relaxation eventually predisposing to the development of diastolic dysfunction[37].

Diabetes mellitus:

Diabetes mellitus is a common risk factor for development of heart failure and it can cause both systolic and diastolic heart failure.

The structural changes in the diabetic heart include myocyte hypertrophy, increased extracellular matrix (fibrosis), and intramyocardial microangiopathy. Functional changes impaired endothelium vasodilation, impaired LV relaxation, increased passive diastolic stiffness, and contractile dysfunction[38].Increase in advanced glycation end products, which promote increased collagen accumulation and increased collagen stiffness. Accumulation of advanced glycation end products may play a role in age-related cardiac and vascular stiffening.

Coronary Artery Disease

Prevalence of ischemic heart disease in patients with DHF varies widely. Ischemic cardiomyopathy decreases the chamber compliance and impairs relaxation, thereby causing diastolic dysfunction[39].

Renal Dysfunction

Effect of renal dysfunction on the outcome of patients with heart failure is well documented[40]. Acute decompensated heart failure due to diastolic dysfunction can occur due to flash pulmonary edema in patients with bilateral renal artery stenosis. In a patient presenting with the triad of hypertension, renal dysfunction, and diastolic, renal Doppler should be done.

Rarer Causes of DHF:

Hypertrophic obstructive cardiomyopathy, amyloidosis, and constrictive pericarditis are possibilities to be considered in differential diagnosis in a younger individual with symptoms suggestive of diastolic heart failure.

Idiopathic restrictive cardiomyopathy in young person usually has positive family history. Radiation can cause damage to both pericardium and myocardium and lead to persistent HF.

Clinical Features of Diastolic Heart Failure

There is no big difference between the signs and symptoms of diastolic and systolic failures only the percentages differ. Mostly diastolic dysfunction is asymptomatic. In majority of cases the first noticed symptom is exercise intolerance, followed by paroxysmal nocturnal dyspnoea, and orthopnoea[41].

Comparison of signs and symptoms in SHF and DHF

Symptoms	DHF	SHF
Exertional dyspnea	85%	96%
Paroxysmal nocturnal dyspnea	55%	50%
Orthopnea	60%	73%
Physical examination		
Jugular venous distension	35%	46%
Displaced apical impulse	50%	60%
S3	45%	45%
S4	45%	66%
Hepatomegaly	15%	16%
Oedema	30%	40%
Cardiomegaly	90%	96%
Pulmonary venous hypertension	75%	96%

Only paroxysmal nocturnal dyspnea is relatively more common in DHF than SHF. All other signs and symptoms are more common in SHF.

DIAGNOSTIC CRITERIA FOR DIASTOLIC HEART FAILURE

Definitive DHF	Probable DHF	Possible DHF
Definitive evidence of Congestive cardiac failure	Same as definitive	Same as definitive
and	and	And
Objective evidence of normal systolic function	Same as definitive	LV EF of 50% or more not measured within 72 hrs of the event
and	and	And
Objective evidence of diastolic dysfunction	No conclusive evidence of DD	Same as probable

Patients who have definitive evidence of congestive cardiac failure and objective evidence of normal LV systolic function are accepted as having probable diastolic heart failure provided valvular and other non-cardiac causes have been excluded.

ASSESSMENT OF DIASTOLIC FUNCTION

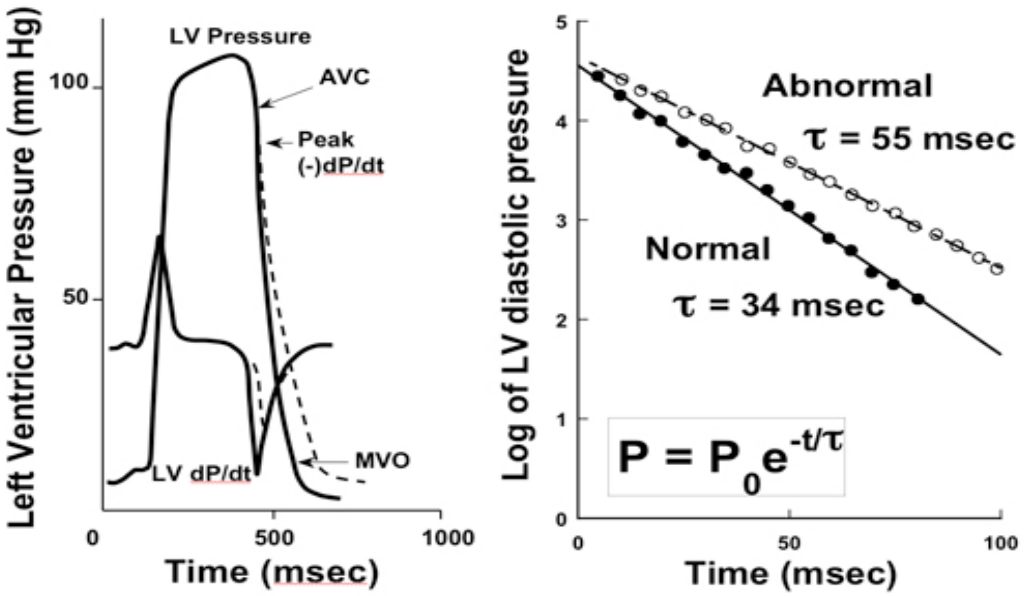
The study of LV diastolic properties requires simultaneous measurement of pressure and volume. Both invasive and non-invasive methods can be used. Invasive methods using high-fidelity micromanometer provides the most comprehensive evaluation. But for practical feasibility non-invasive methods such as Doppler echocardiography are used.

Changes in both afterload and diastolic load can affect measurements of diastolic function. These load-dependent changes do not reflect alteration in intrinsic relaxation properties.

Rate of isovolumic relaxation: The rate of LV pressure decline, or the rate of isovolumic relaxation, reflects early diastolic function. Accurate assessment requires a high-fidelity micromanometer catheter. Measures of this property include:

- Peak dP/dt: Peak negative dP/dt is the peak instantaneous rate of LV pressure decline.
- Tau (τ): Tau is the time constant of isovolumic LV pressure decay[42]. Tau is the slope formed when log value of left ventricular diastolic pressure is plotted against time. Tau is the time taken for the left ventricular pressure to reduce by more than 66%.

- Isovolumic relaxation time (IVRT): IVRT can be measured with noninvasive echocardiographic techniques. Isovolumic relaxation time (IVRT) is an interval between the aortic valve closure to opening of the mitral valve. It can be used as an indicator of diastolic dysfunction. Normal IVRT is 70 ± 12ms. In abnormal relaxation, IVRT exceeds 110 ms[43].



When the relaxation rate is decreased (ie, abnormal diastolic function), Tau is increased and the absolute value of the peak negative dP/dt is reduced. IVRT increases with impaired relaxation but then decreases with progressive worsening of diastolic function[44].

Rate and extent of LV filling: The normal LV has a characteristic pattern of filling and transmitral inflow velocities. A number of measures characterize the rate of LV filling, including:

- LV filling rate
- The time-to-peak-filling rate (TPFR) Transmitral flow velocity
- Diastolic suction (flow propagation velocity)
- Pulmonary venous flow velocities
- Myocardial tissue velocity, strain, and strain rate.

There are four patterns of diastolic function that can be identified using transmitral Doppler spectral recordings, color Doppler M-mode inflow propagation velocities, pulmonary vein Doppler flow measurements, and tissue Doppler echocardiography namely: normal, impaired relaxation, pseudonormal, and restrictive[45].

Echocardiography: Echocardiography gives useful information about chamber size, valve morphology, and systolic function. 2D echocardiography is helpful in assessing the diastolic phase of cardiac cycle.

Transmitral flow velocity: E-wave denotes the early diastolic peak filling velocity and A-wave the late diastolic peak filling velocity. Former depends on the transmitral pressure gradient and latter on the atrial contraction.

E-wave is normal taller than the A-wave and hence the ratio is >1. There reversal of this ratio occurs in the initially stages of diastolic dysfunction.

Progression of the diastolic dysfunction causes more reduction in compliance and increases the left atrial pressure, this causes the ratio to normalize. This is called pseudonormalization. This is the drawback of using E/A ratio, but this can be neutralized by using Valsalva maneuver or GTN administration during the procedure.

Pulmonary venous flow: Normally there is a forward flow of blood from left atrium to left ventricle during atrial relaxation and left ventricular diastole, and there is minimal back flow during atrial contraction. In diastolic dysfunction this back flow of blood into the pulmonary veins becomes exaggerated.

Isovolumetric relaxation time(IVRT): IVRT extends from aortic valve closure to mitral valve opening. Normal IVRT is 70±12ms. It is a good indicator of diastolic function. In diastolic dysfunction the IVRT becomes more than 110ms.

Deceleration time (DT): It is the time taken for the fall in transmitral pressure gradient. Normal value is 180-240ms. In the initial stages of diastolic dysfunction the DT is prolonged, but it becomes shortened due to the hike in left atrial pressure in later stages.

Tissue Doppler: Tissue Doppler helps to calculate the velocity of myocardial tissue movement using the Doppler shift of ultrasound waves. Following velocities can be calculated namely:

E´ wave: Peak early diastolic mitral annular velocity

A´ wave: Late diastolic mitral annular velocity.

LV long-axis lengthening velocity during diastole parallels patterns found in transmitral diastolic inflow. In the normal heart, the rate of lengthening is greatest early in diastole immediately after mitral valve opening, as reflected by a tall E´. Lengthening resulting from atrial contraction at the end of diastole is relatively small reflected by a relatively small A´.

GRADES OF DIASTOLIC DYSFUNCTION

- **Grade I diastolic dysfunction** (impaired relaxation): When diastolic dysfunction initially occurs, relaxation is slowed and incomplete as reflected by an increased isovolumic relaxation time. This results in an increase in early LV diastolic pressures, a decrease in the early transmitral pressure gradient, and a decrease in diastolic suction as reflected by a decrease in color M mode flow acceleration. LV filling is abnormal with decreased early filling rate and extent, prolonged TPFR,

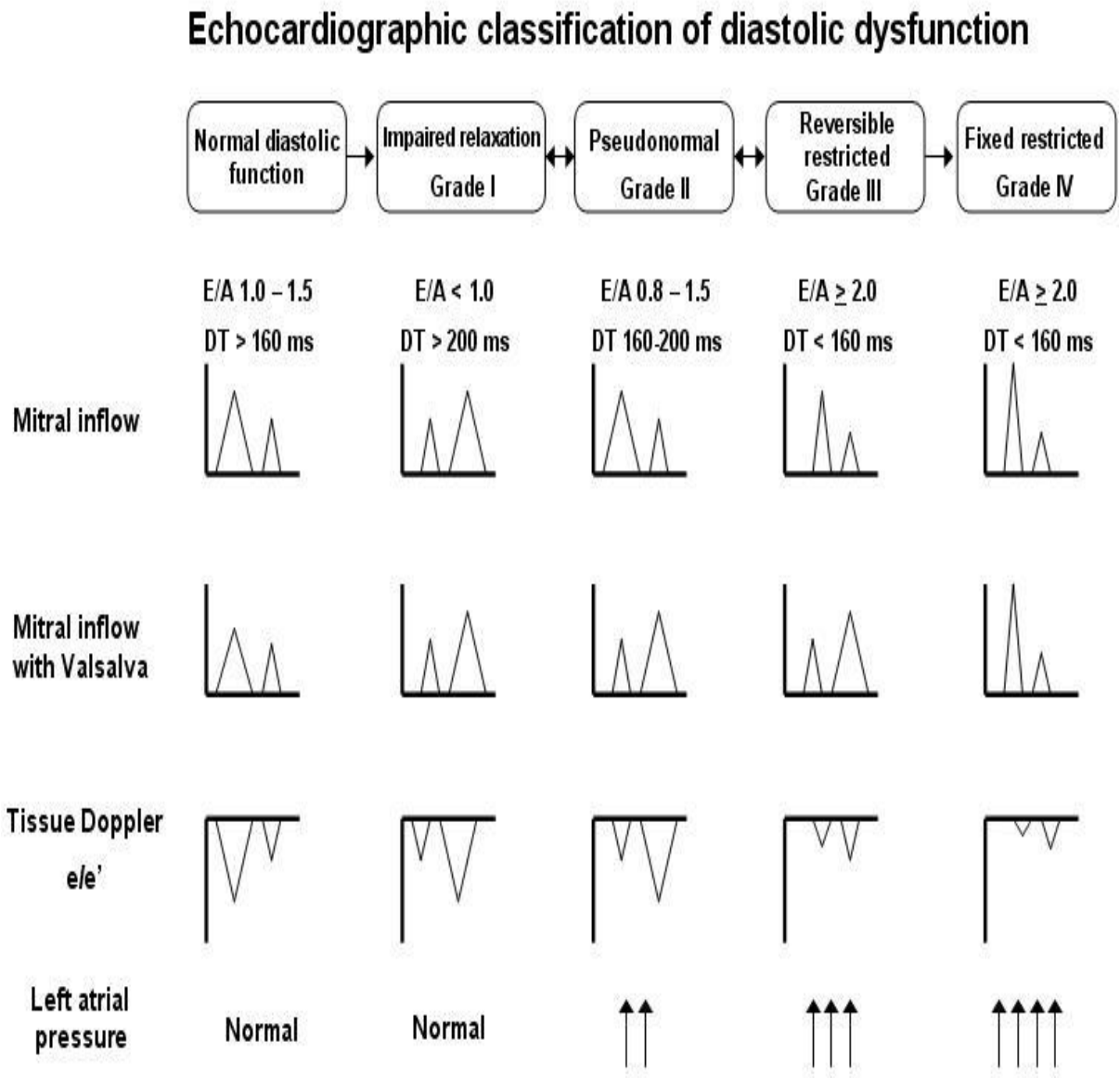
increased filling rate from atrial contraction, and thus, a decreased E/A ratio (A dominant pattern). Tissue Doppler myocardial lengthening velocity patterns are similar to the transmitral flow velocities, with E' reduced and A' increased.

- **Grade II diastolic dysfunction** (pseudonormal): As diastolic dysfunction progresses, LV filling becomes increasingly dependent upon an increase in LA pressure to push blood into the LV during diastole .As LA pressures rise, the early diastolic transmitral pressure gradient increases, early diastolic flow velocities also rise and the E wave increases, causing the E/A ratio to increase to a "normal" (or pseudonormal) value.

  However, myocardial velocity by tissue Doppler echocardiography is less sensitive to alteration in LV loading conditions than transmitral Doppler velocities and E' (the rate of early diastolic myocardial lengthening) remains markedly reduced.

  Thus, varying combinations of alterations in E and E´ help to distinguish impaired relaxation and pseudonormal patterns from a normal pattern. Impaired relaxation has low E/E´ ratio, where as in pseudonormal pattern the ratio can be normal or increased because E´ is very much reduced[46].

- **Grades III and IV diastolic dysfunction** (restrictive): If left atrial pressures are severely increased, a "restrictive" pattern may develop in which the isovolumic relaxation time may be decreased, transmitral pressure gradient is further increased and the E/A and E/E' ratios are markedly increased to supernormal levels. This restrictive pattern is characteristic of marked elevations in filling pressure with grade III (reversible restrictive pattern) or grade IV (irreversible restrictive pattern) diastolic dysfunction [47].



TREATMENT OF DIASTOLIC HEART FAILURE

Treatment has got two objectives. First to immediately relieve the symptoms and to eliminate the precipitating factors. Next to reverse the factor responsible for the diastolic dysfunction. Both nonpharmacologic and pharmacologic therapy can be used to achieve these objectives.

Symptomatic Therapy
Reduce pulmonary venous pressure Improve exercise tolerance[48] inotropic agents
Non-pharmacological Therapy
Salt and fluid restriction Aerobic exercise
Pharmacological Therapy Diuretics, including loop diuretics, thiazides, spironolactone Long-acting nitrates β-Adrenergic blockers Calcium channel blockers[49] Renin-angiotensin-aldosterone antagonists, including ACE inhibitors, angiotensin II receptor blockers, and aldosterone antagonists
Treatment of underlying conditions
Preventing myocardial ischemia control of hypertension, diabetes

GENERAL APPROACH

Primary prevention includes quitting of smoking and optimal control of high blood pressure, diabetes mellitus, dyslipidemia, and ischemic heart disease**.**

Apart from quitting smoking, other life style modifications such as weight reduction, dietary changes, controlling alcohol consumption, and aerobic exercise help to prevent not only systolic failure but also diastolic failure.

Diastolic dysfunction remains asymptomatic for many years. Hence, early diagnosis and treatment is critical to prevent irreversible morphological alterations.

There is no specific drug till date for the management of diastolic heart failure. There are well defined therapeutic options available for systolic failure but for diastolic failure treatment is mainly empirical.

The treatment of diastolic heart failure is limited by the lack of data from definite well defined studies.

Heart Failure: Treatment Goals

Underlying disease Treatment Prevent and treat hypertension, diabetes mellitus and ischemic heart disease. Surgically remove diseased pericardium
left ventricular relaxation improvement Calcium channel blockers ACE inhibitors
Regress left ventricular hypertrophy Beta blockers ACE inhibitors and ARBs Aldosterone antagonists Calcium channel blockers
Management of arrhythmias Beta blockers Calcium channel blockers Digoxin[50] Atrioventricular node ablation
Reducing mortality ACE inhibitors Beta blocker

Differences in the treatment of Systolic and diastolic heart failure

The drugs being used in the treatment of DHT are more or less same as those used in the SHF treatment. But the internal mechanism that the drug alters are different as well as the dosages required.

For example, beta-blockers decrease the heart rate and help to increase the duration of diastole in DHF, while in SHF on a long term basis increase the inotropic activity and alter the LV remodeling. In the case of SHF the titration of beta-blockers must be done gradually unlike in DHF.

Diuretics are useful in both SHF and DHF. But smaller doses are sufficient in case of DHF.

Calcium channel blockers have no role in the treatment of SHF, but in DHF they improve left ventricular relaxation and regress the LVH.

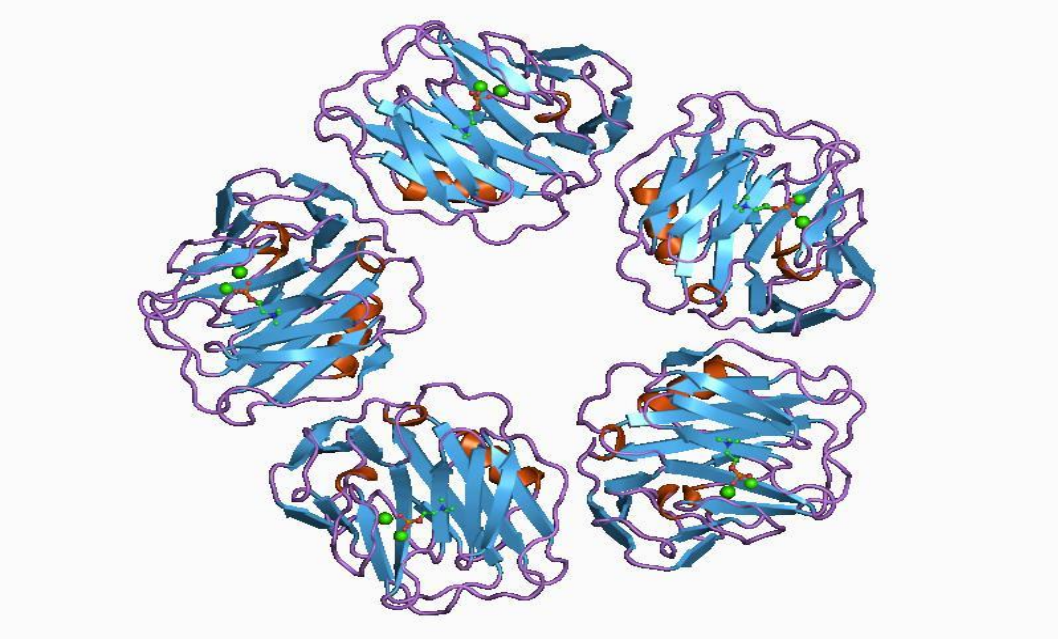
Future perspectives:

Ideally the therapeutic agent must block the underlying mechanisms causing the diastolic dysfunction. For example it must improve the calcium homeostasis and energetic, and should stop and decrease the amount of fibrosis. Unfortunately no such drugs are available at the moment.

C-REACTIVE PROTEIN

C-reactive protein (CRP) is a protein produced in the liver[51] in response to inflammation occurring anywhere in the body. It is better known as an acute-phase reactant. Its binds to phosphocholine expressed on the surface of dead or dying cells resulting in the activation of the complement system through the C1Q complex[52].

CRP is synthesized in response to factors released by macrophages and adipocytes. It belongs to the pentraxin family of proteins[53]. It was the first pattern recognition receptor (PRR) to be identified[54].



Structure of C - reactive protein

CRP was first identified in the serum of patients with acute inflammation as a substance that reacted with the C-polysaccharide antigen of Pneumococcus. It was discovered by Tillett and Francis in 1930[55]. The CRP gene is located on chromosome one (1q21-q23).

Biological Role:

Acute phase response occurs in wide variety of conditions like infections, inflammatory states and malignancies. These conditions cause increase in interleukin-6 and other cytokines in the body, which in turn cause the liver to produce c-reactive protein.

CRP levels start to increase within two hours of acute inflammation, reaching its maximum level within 48 hrs, when the inflammation subsides it returns to baseline within 18 hrs.

CRP binds to phosphocholine on microbes and necrotic cells and facilitates phagocytosis by macrophages. In this way CRP helps in the clearance of necrotic and apoptotic cells.

CLINICAL SIGNIFICANCE

CRP is a very valuable biomarker of inflammation.

CRP levels can be estimated by many analytical methods namely ELISA, laser nephelometry, immunoturbidimetry, rapid immunodiffusion, and visual agglutination.

The reference range for C-reactive protein is 0-10mg/dl [49].

Conditions associated with high CRP levels (>10 mg/L) are

Inflammation – autoimmune disorders, rheumatoid arthritis, vasculitis
Infection -bacterial sepsis or fungal infection
Acute coronary syndromes

CRP ranges in different conditions[56]:

Conditions	CRP Values
Mild inflammation and viral infections	(10–40 mg/L)
Active inflammation, bacterial infection,	(40–200 mg/L)
Severe bacterial infections and burns	(>200 mg/L)

CRP AND CARDIOVASCULAR DISEASE

High-sensitivity CRP assays measure very low levels of CRP in the blood. The two popular methods are laser nephelometry and immunoturbidometry. These assays can measure CRP to the level upto 0.04 mg/L.

Hs-CRP plays a major role in the cardiovascular risk stratification.

The American Heart Association has defined risk groups as

Low Risk: < 1.0 mg/L

Average risk: 1.0 - 3.0 mg/L

High risk: > 3.0 mg/L

Ridker et al. 2000 and Olsen et al. 2008 showed that hs-CRP could be used to predict cardiovascular events in the general population.

Torwezki et al. 1998 and Zwaka et al. 2001 found that hs-CRP could play a role in the pathogenesis of atherosclerosis.

AIMS AND OBJECTIVES

Primary Objective: To screen for the presence of diastolic dysfunction in patients with cardiovascular risk factors, and to measure their serum hs-CRP levels.

Secondary Objective: To study the association between the hs-CRP levels and diastolic dysfunction in the patients with cardiovascular risk factors.

MATERIALS AND METHODS

SOURCE OF DATA: Data was collected from out patients with cardiovascular risk factors attending Rajiv Gandhi Government General Hospital.

STUDY DESIGN: Cross-sectional study

SAMPLE SIZE: 100 patients.

Duration: 6 months (June 2013-Nov 2013)

METHOD OF COLLECTION OF DATA:

After obtaining informed consent the patients were subjected to detailed history, clinical examination and investigations as per the proforma. Institutional Ethics Committee clearance was obtained. The following criteria were applied for selection of patients in the study group.

Inclusion Criteria :

Known cases of

- Hypertension,
- Type 2 diabetes mellitus,
- Dyslipidemia

who are under medications.

Exclusion Criteria:

Patients with

- History or clinical evidence of heart failure,
- History of cardiovascular disease such as coronary artery disease, valvular heart disease, arrhythmias, stroke, peripheral vascular disease),
- Newly diagnosed diabetes mellitus and hypertension(<1year)
- Renal failure with serum creatinine > 1.6
- Chronic alcoholism
- History or clinical evidence of recent or acute systemic infection/inflammation.

METHODOLOGY:

After obtaining informed consent from the enrolled patients, a questionnaire was prepared to obtain details of the patients name, age, sex occupation and symptoms if any. History suggestive of heart failure was given due importance. Vital parameters of the patients were recorded. Height and weight of the patients were measured to calculate the Body mass Index (BMI). The body mass index was calculated using the formula Body mass index = weight of the patient (kg) / $(height)^2$ (height in metres). Routine clinical examination was done.

All the patients were subjected to the following investigations

- Blood urea nitrogen
- Serum creatinine
- Fasting blood sugar
- Fasting lipid profile.
- Complete hemogram
- Plasma hs-CRP
- ECG
- Echocardiography

For the measurement of hs-CRP 5ml of venous blood was collected in a red top vacutainer tube and analysed in Cobas Integra 400 analyser by using immunoturbidometric method.

ASSESSMENT OF DIASTOLIC DYSFUNCTION:

All patients enrolled in the study were subjected to echocardiography. Transthoracic echocardiography was done after clinical evaluation. Echocardiography was done using Philips HD 7 echocardiography machine and systolic and diastolic functions were analyzed.

2D echocardiography was done to assess the ventricular dimensions, presence of regional wall motion abnormalities and left ventricular ejection fraction. The parasternal and long axis view were used. Ejection fraction was calculated using Simpson’s approach.

Doppler echocardiography was done and using the apical four chamber view, the transmitral flow velocities were obtained by positioning the sample volume at the level of the tips of the mitral leaflets. The early mitral inflow velocity (E) and late inflow velocity (A) were obtained, and E/A ratio was calculated.

E/A ratio of less than 1 was considered as grade I diastolic dysfunction. When E/A ratio was more than 1, additional parameters like the velocity propagation, E wave deceleration time were considered to differentiate grade II diastolic dysfunction from normal pattern. The velocity propagation of the early mitral inflow was assessed using a color M mode echocardiography.

Data obtained by the above methods were analyzed using IBM SPSS 20 software package.

OBSERVATION & ANALYSIS

PATIENT CHARACTERISTICS:

Table 1. Sex Distribution:

Among the 100 patients enrolled in the study, 56 were male and 44 were female patients.

Table1: Sex distribution:

Sex	No. of patients(n=60)	Percentage
Males	56	56%
Females	44	44%

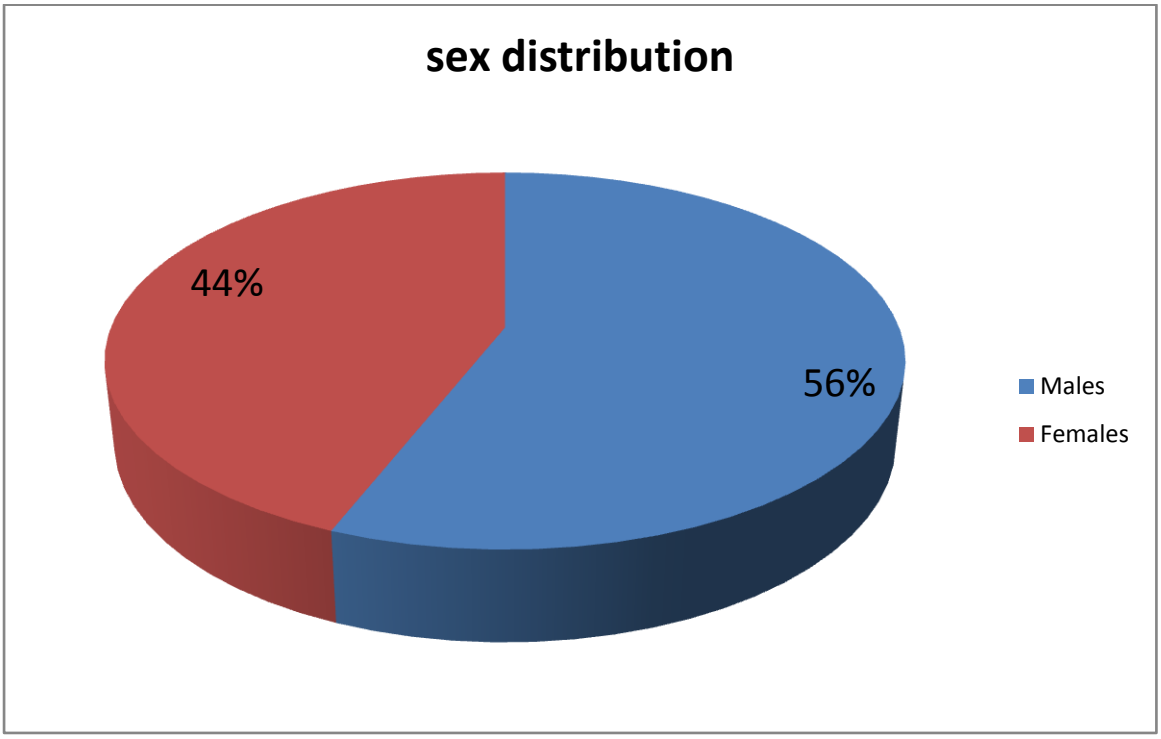


Table 2. Age distribution:

Out of the 100 patient in the study the youngest patient was 30 years old and oldest patient was 75 years old. The no of patients were maximum in the 51-60 age group. The mean age of the patients was 52.92 with a standard deviation of 10.54

Age distribution	No of patients(n=100)	Percentage
30-40 yrs	12	12%
41-50yrs	31	31%
51-60yrs	40	40%
>60yrs	17	17%

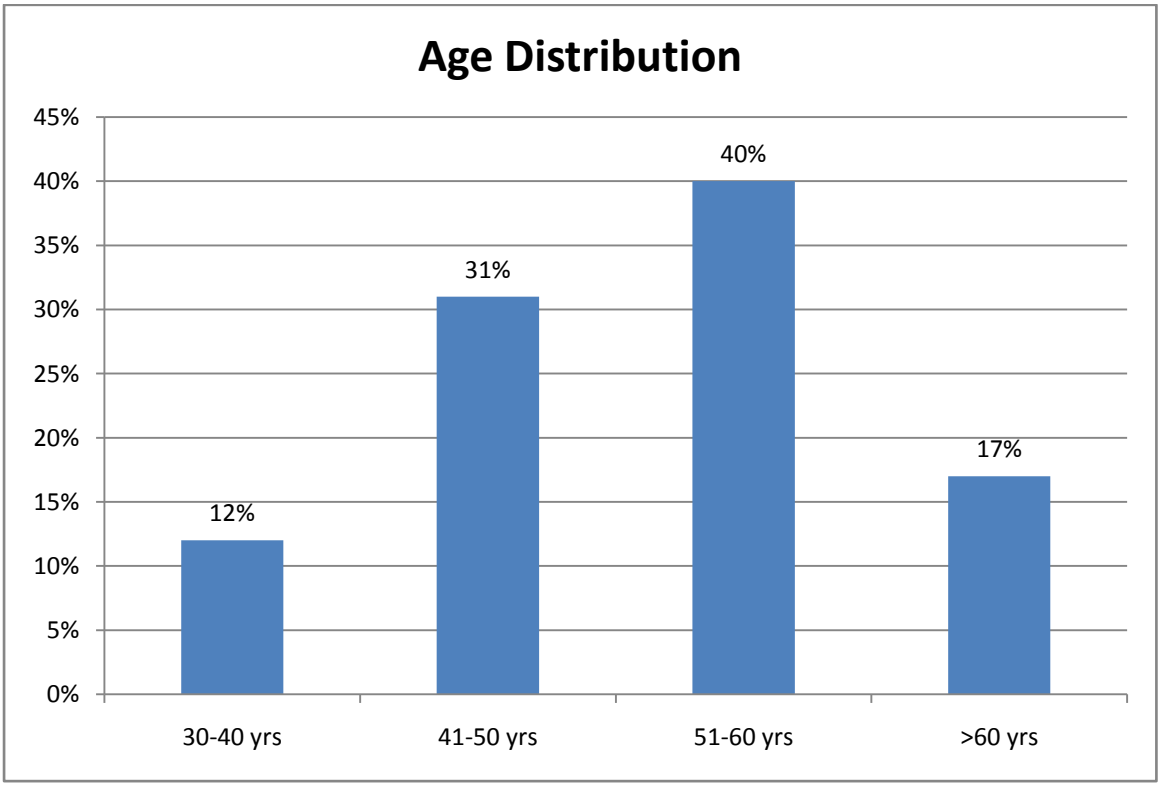


Table 3. Distribution of Cardiovascular risk factors:

100 patients enrolled in the study were divided into six group depending upon the presence of cardiovascular risk factors, maximum no of patients were in C-group which included patients with HT AND DM.

Distribution of cardiovascular risk factors.

Group	Risk Factors	No. of patients(n=100)	percentage
A	HT	20	20%
B	DM	20	20%
C	HT+DM	22	22%
D	HT+DL	10	10%
E	DM+DL	14	14%
G	HT+DM+DL	14	14%

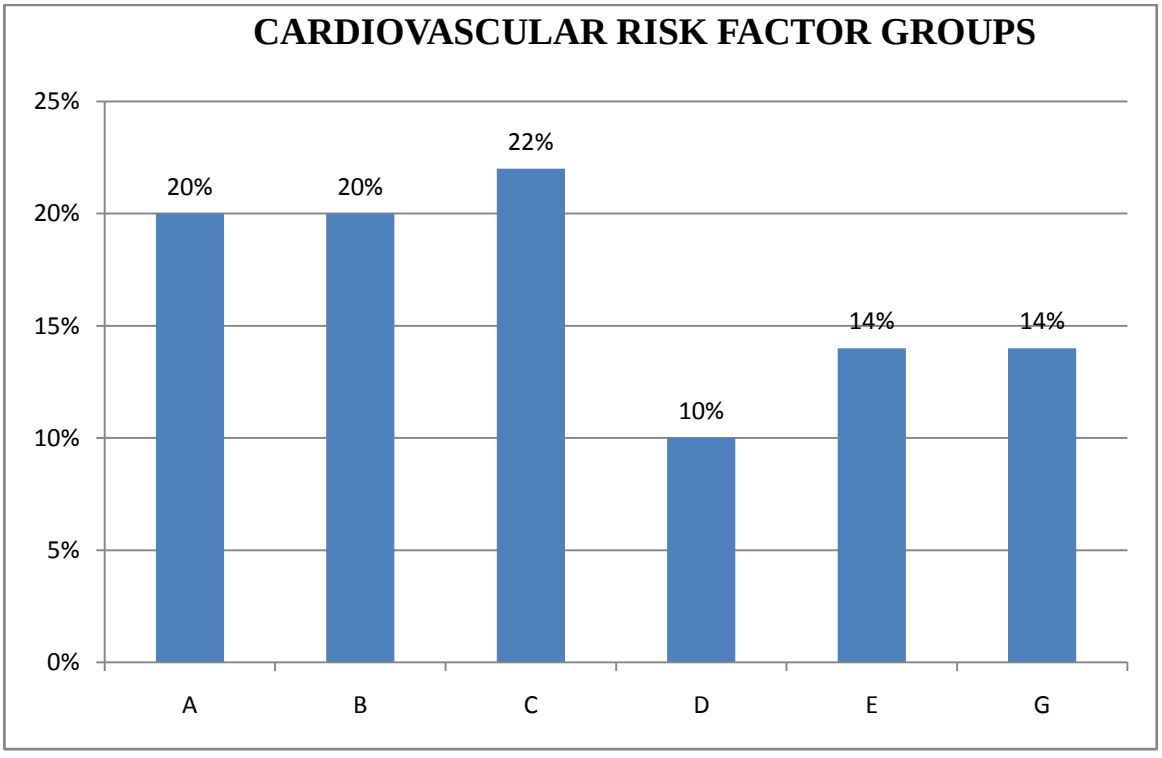
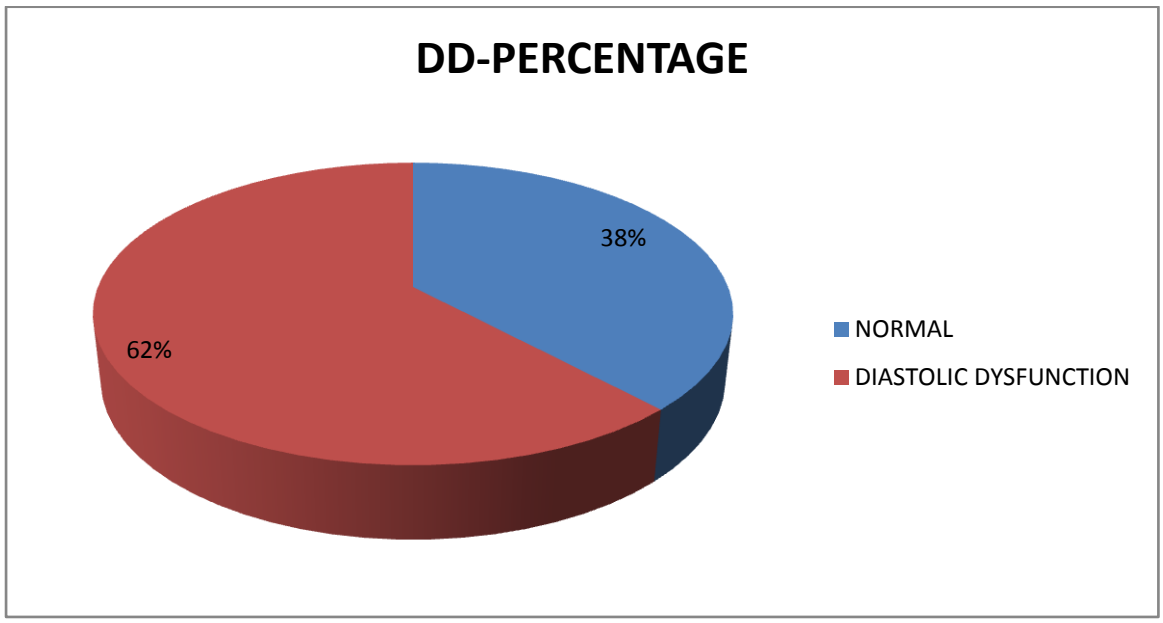


Table 4. PREVALENCE OF DIASTOLIC DYSFUNCTION

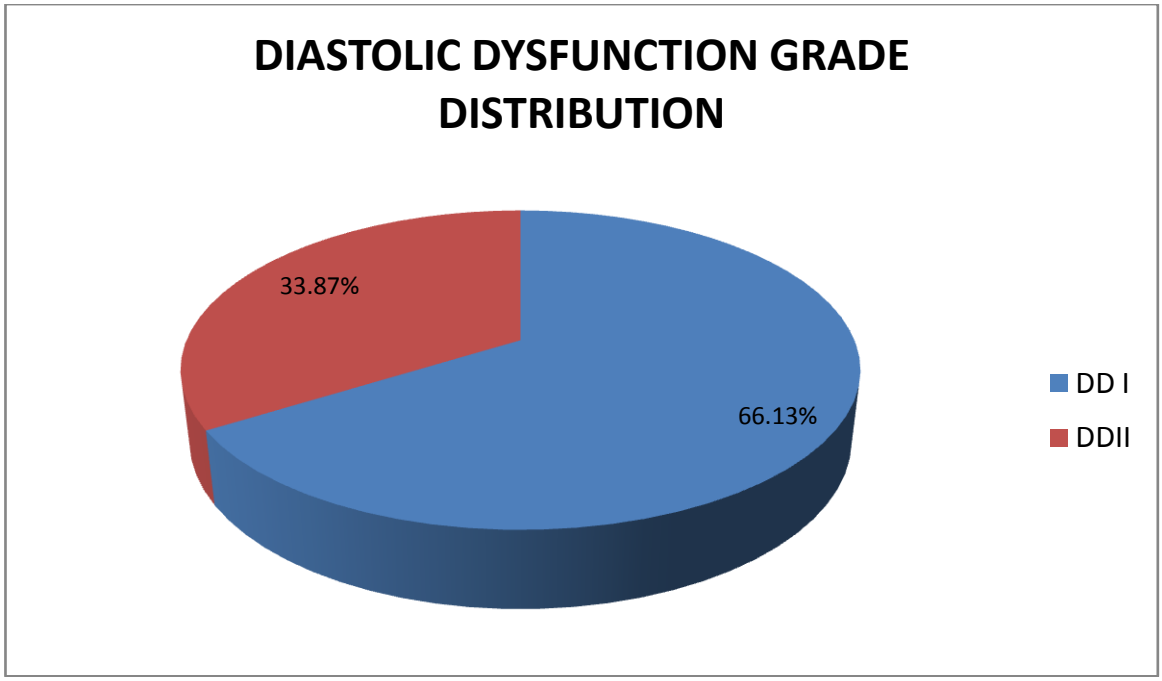
Among the 100 patients in the study 62 had echocardiographic evidence of diastolic dysfunction. 41patients had Grade I DD and 21 patients had Grade II DD.

There was no Grade III or Grade IV DD observed. All patients had EF>50%.

None of the patients had clinical evidence of heart failure.



DD-GRADE	NO OF PATIENTS(n=62)	PERCENTAGE
DD I	41	66.13%
DD II	21	33.87%


DIASTOLIC DYSFUNCTION GRADE DISTRIBUTION
33.87%
66.13%
DD I
DDII

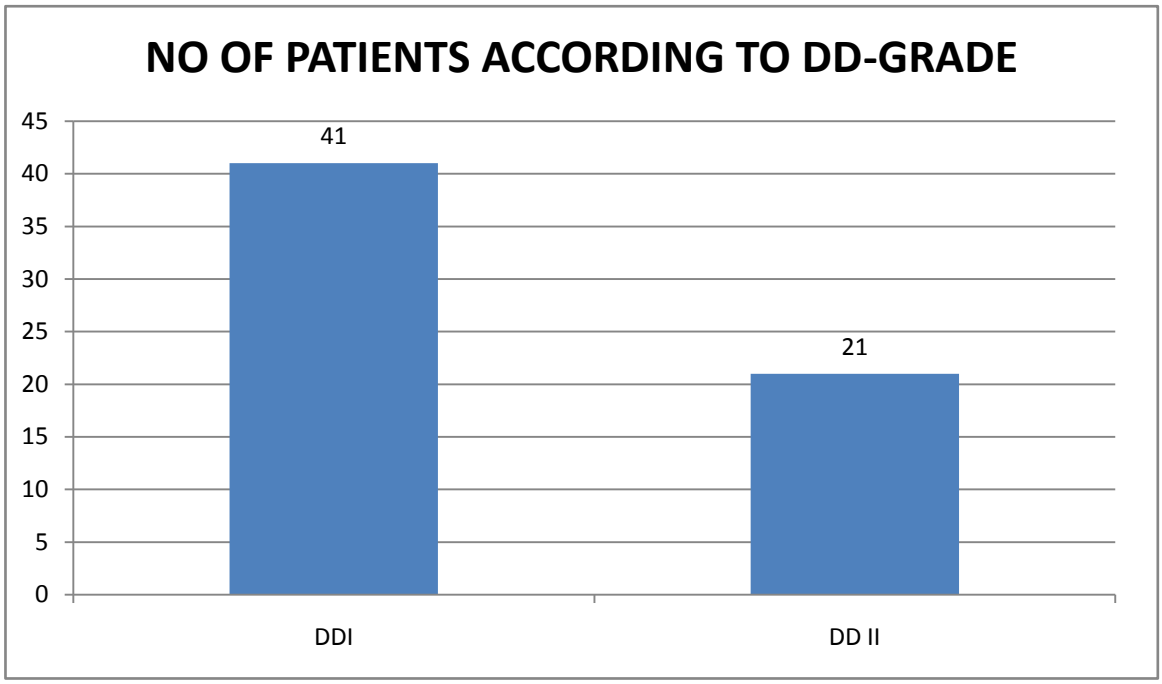

NO OF PATIENTS ACCORDING TO DD-GRADE
45
40
35
30
25
20
15
10
5
0
41
21
DDI
DD II

Table 5. AGE AND DIASTOLIC DYSFUNCTION:

The prevalence of diastolic dysfunction increases with age. In our study highest percentage of diastolic dysfunction was observed in above 60 age group. 30-40 age group had the lowest percentage.

AGE GROUP(n=100)	No of patients with diastolic dysfunction(n=62)		PERCENTAGE
	Grade I	Grade II	
30-40years(n=12)	2	0	16.67%
41-50years(n=31)	10	0	32.26%
51-60 years(n=40)	25	9	85.00%
Above 60(n=17)	4	12	94.12%

By Pearson Chi square test, for the above values **p value < 0.001**** significant at 1% level. Correlation co-efficient between age and hs-CRP was r = 0.593, which is positive correlation.

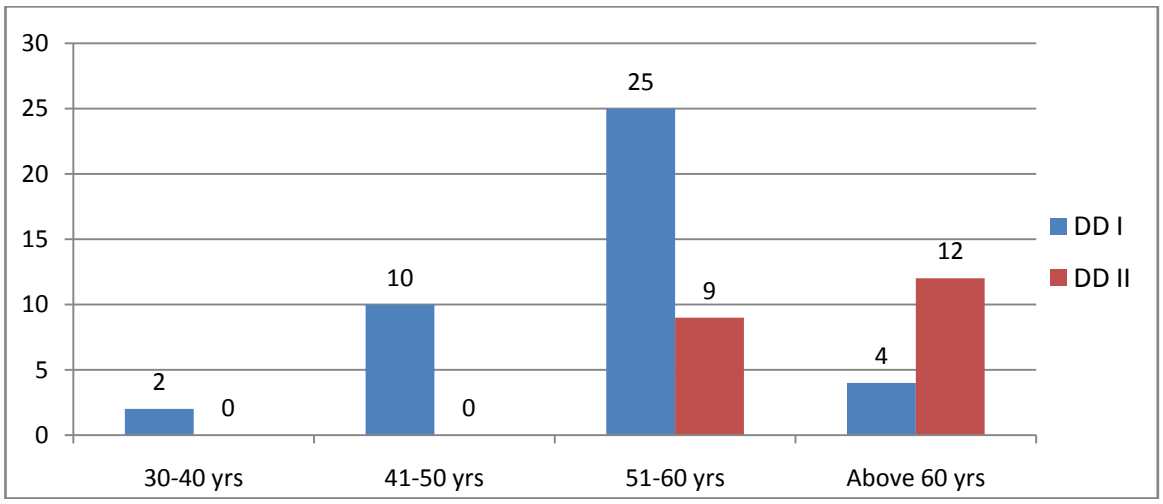
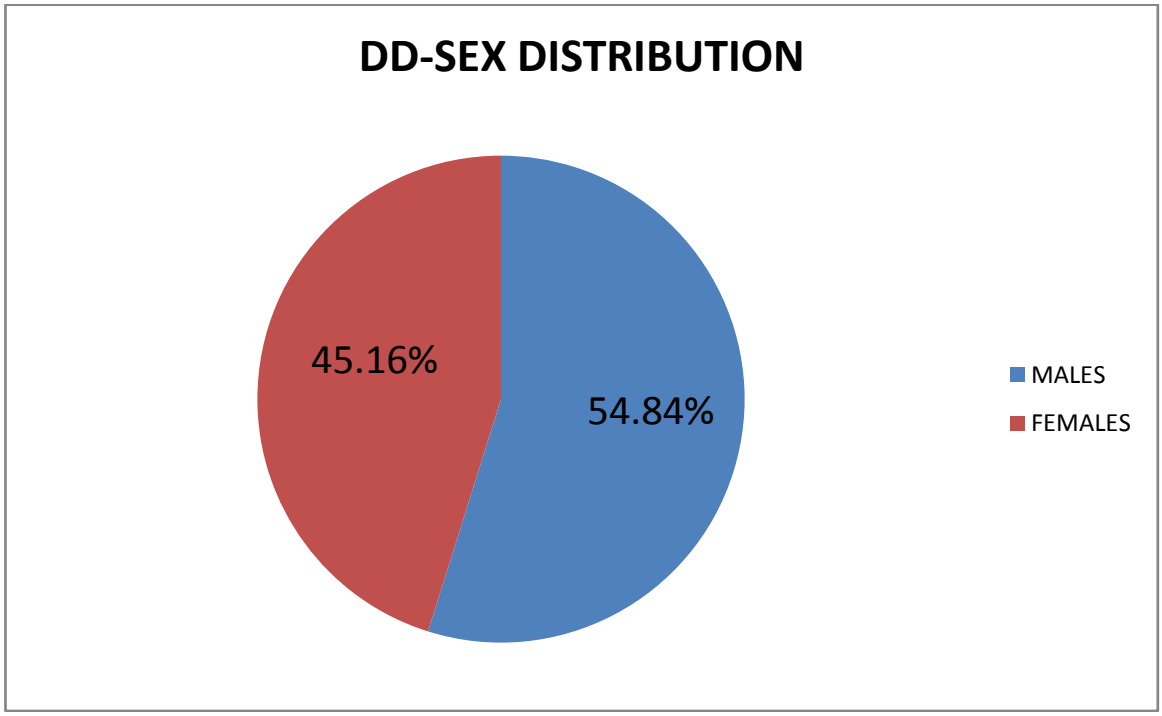


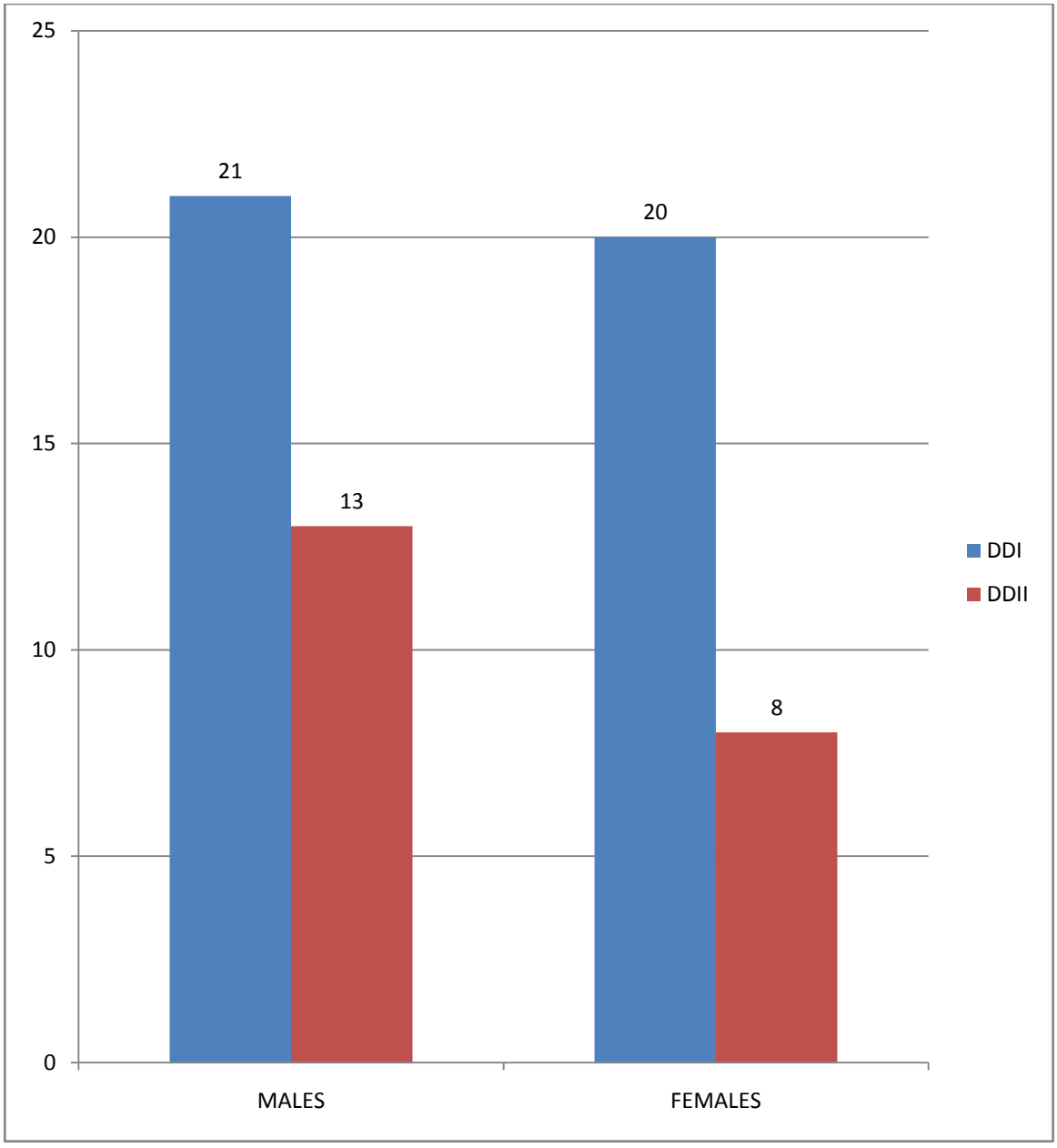
Table 6. SEX AND DIASTOLIC DYSFUNCTION:

Out of the 56 males 34 patients had diastolic dysfunction and in females patients 28 had diastolic dysfunction. Percentage was slightly higher in the female patients.

SEX(n=100)	No of patients with diastolic dysfunction(n=62)		PERCENTAGE
	Grade I	Grade II	
Male(n=56)	21	13	60.71%
Female(n=44)	20	8	63.63%

By Pearson Chi square test, for the above values **p value = 0.693,** statistically not significant.





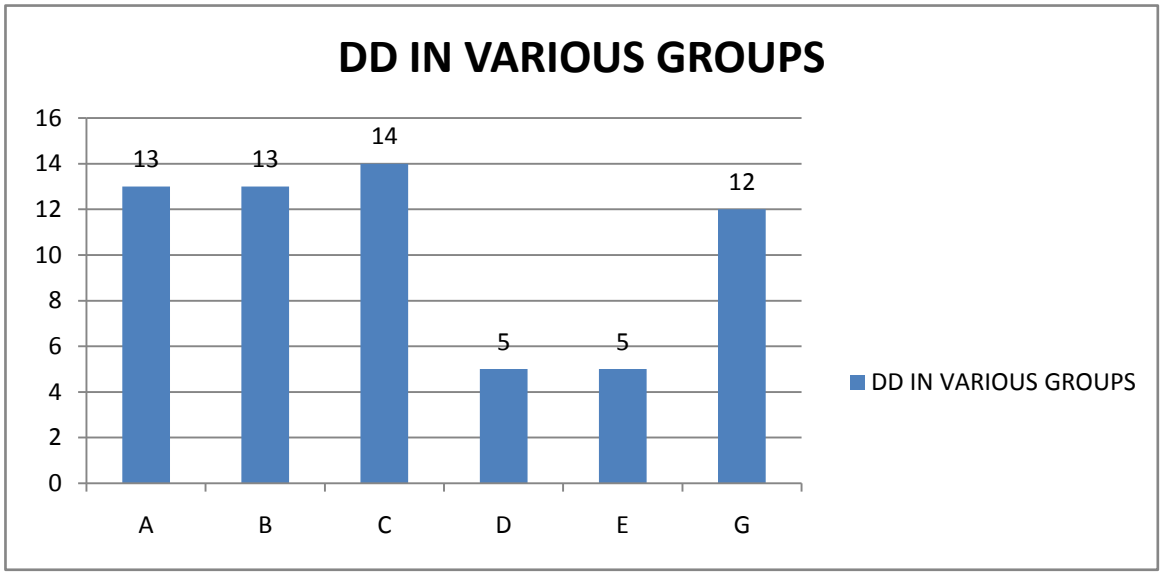
DISTRIBUTION OF DD-GRADES IN BOTH SEXES

Table 7. DISTRIBUTION OF DIASTOLIC DYSFUNCTION AMONG VARIOUS RISK FACTORS GROUPS

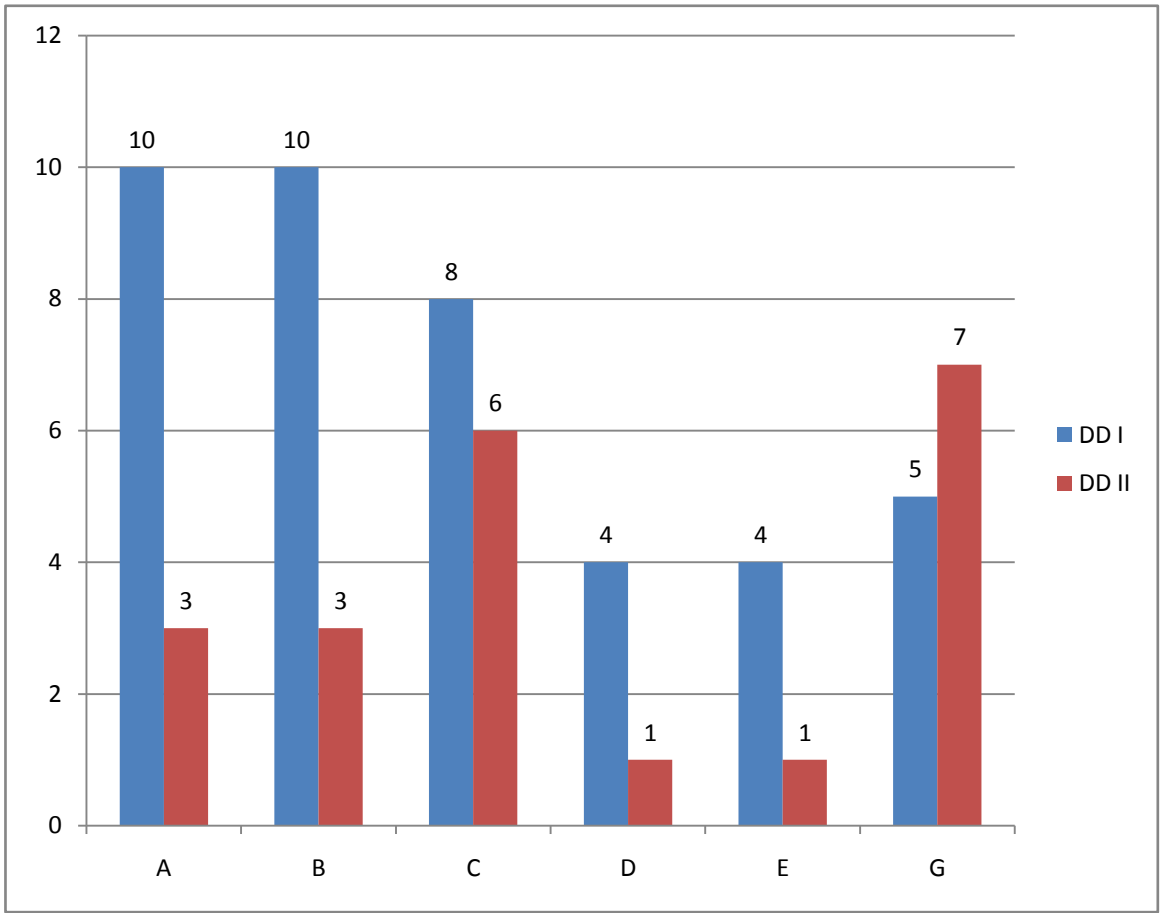
Patients were divided into six risk groups.

Group	Risk Factors	No of patients with diastolic dysfunction(n=62)		PERCENTAGE
		Grade I	Grade II	
A(n=20)	HT	10	3	65%
B(n=20)	DM	10	3	65%
C(n=22)	HT+DM	8	6	63.64%
D(n=10)	HT+DL	4	1	50%
E(n=14)	DM+DL	4	1	35.71%
G(n=14)	HT+DM+DL	5	7	85.71%

By Pearson Chi square test, for the above values **p value = 0.125,** statistically not significant.



Grades of DD in various Risk Factor Groups



Patients who had hypertension, diabetes mellitus and dysplipidemia had highest percentage of DD. Patients with diabetes and dyslipidemia had the least

Percentage of DD. In patients who had only hypertension or diabetes the prevalence of DD was equal.

Table 8. Body Mass Index and Diastolic Dysfunction:

BMI was calculated for all the patients using the formula BMI = W/H^2 were W is the weight is kilograms and H is the height in metres.

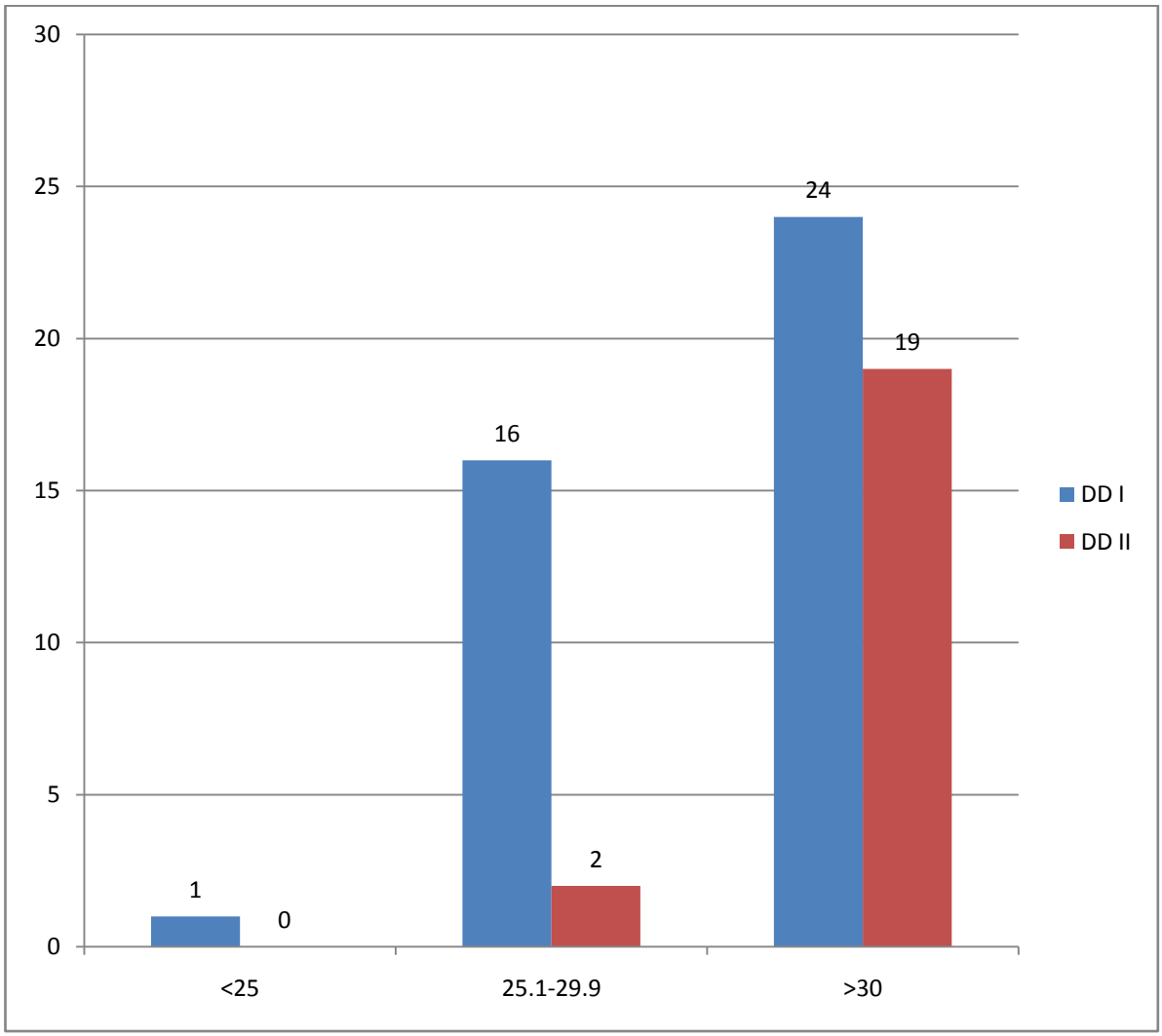
The mean was 30.68 and the standard deviation was 2.98.

The minimum value was 23.4 and the maximum value was 36.4

BMI (n=100)	No of patients with diastolic dysfunction (n=62)		Percentages
	Grade I	Grade II	
<25 (n=4)	1	0	25.00%
25-29.9(n=43)	16	2	41.86%
≥30(n=53)	24	19	81.13%

By Pearson Chi square test, for the above values **p value < 0.001**** significant at 1% level.

Correlation co-efficient between BMI and hs-CRP was r = 0.538, which is positive correlation.



BMI AND DIASTOLIC DYSFUNCTION

X-axis – BMI

Y-axis – DD

According to our study there was statistically significant association between the BMI and DD

Table 9. hs-CRP and Diastolic Dysfunction:

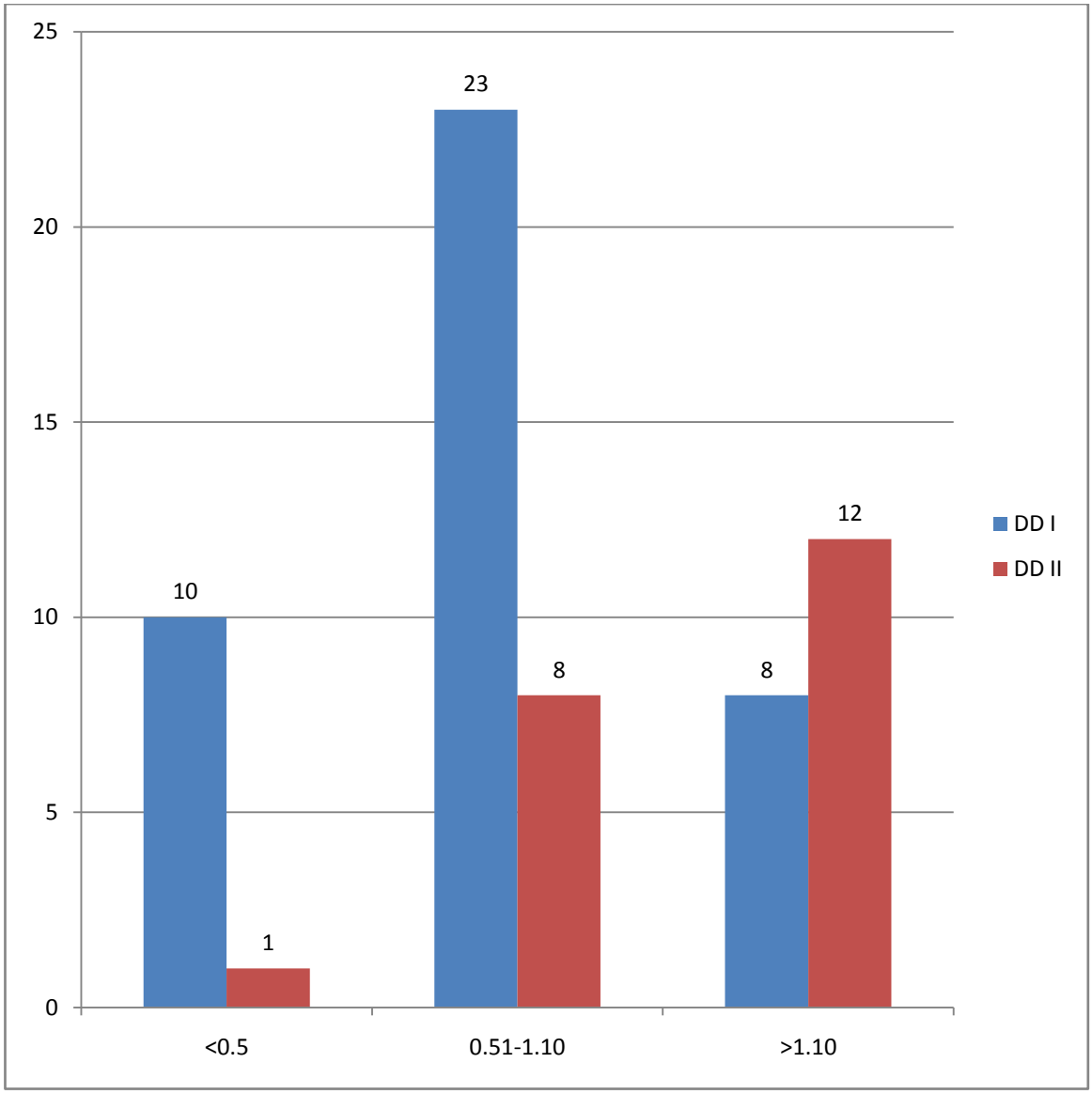
hs-CRP levels were measured for all the patients in the study. The least value recorded was 0.11 mg/dl and the maximum value was 2.36 mg/dl.

The mean value was 0.70 with a standard deviation of 0.52.

hs-CRP values above 0.5mg/dl had significant association with diastolic dysfunction. 53% of patients with DD had values more than 0.5mg/dl

hs-CRP value(n=100) mg/dl	Diastolic dysfunction		PERCENTAGES
	Grade I (n=41)	Grade II (n=21)	
<0.5(n=47)	10	1	23.40%
0.5-1.0(n=32)	23	8	96.86%
>1.1(n=21)	8	12	95.24%

By Pearson Chi square test, for the above values **p value = 0.001**** significant at 1% level.



hs-CRP and Diastolic dysfunction

X-axis: hs-CRP

Y-axis: Diastolic dysfunction

According to our study there was statistically significant association between the hs-CRP and DD

DISCUSSION

Diastolic dysfunction and age:

High statistical significance (**P < 0.001****) was observed for the association between age and diastolic dysfunction.

According to our study increasing age is a risk factor for development of diastolic dysfunction. Above the age of 50 nearly 89% of the patients had diastolic dysfunction. From this it is quite clear that age and diastolic dysfunction have a linear relationship.

Fischer et al. (2002), have reported the prevalence of diastolic dysfunction is more common than systolic dysfunction as the age advances and in the presence of risk factors.

According to Kuznetsova et al. (2009) the prevalence of diastolic dysfunction in general population was as high as 27.3%. The mean age of the patients in the study was 52.7 years.

Arbab-Zadeh et al. 2004 have shown that left ventricular diastolic stiffness is increased in sedentary elderly people when compared to person with active life style and sustained endurance training can preserve the left ventricular compliance with aging.

Diastolic dysfunction and sex:

In our study the prevalence of diastolic dysfunction was slightly higher in females than in males but no underlying causes or mechanisms could be attributed to this difference.

Mohamed et al. (2004) showed that in patients with systemic hypertension the development of development of diastolic dysfunction did not have any particular gender preference.

R. Wachter et al. (2007) showed that the presence of diabetes has an influence on the diastolic function in males but there was no difference in females between the diabetic and non-diabetic population.

Wong et al. (1989) and Ghali et al. (1991) have reported that female gender as a good predictor of development of diastolic dysfunction.

Whereas other studies such as Warnowicz et al. (1983), Dougherty et al (1984), Kinney et al (1989), Cocchi et al (1991)., have not included gender as a positive predictive factor for development of diastolic heart failure.

Diastolic Dysfunction and BMI

High statistical significance (**P < 0.001****) was observed for the association between BMI and diastolic dysfunction.

53% of the patients had BMI more than 30, out of which 83% had diastolic dysfunction. However, these patients had different associated risk factors. Hence obesity alone cannot be fully attributed to the development of diastolic dysfunction.

Recent study Russo C et al. (2011) has shown that increased BMI was associated with poor left ventricular diastolic function which is independent of left ventricular hypertrophy and other associated risk factors.

Persic V et al. (2007) found out that obesity in newly diagnosed hypertensives contributed to the development of diastolic dysfunction.

A large recent Japanese study (n=692) Kinuko Dote et al. (2011) had found a good correlation between obesity and presence of diastolic dysfunction. The mean and standard deviation of the BMI in obese patients was 33.1±3.6kg/m2 with a range of 30.0–44.7 kg/m2. 91% of the obese patients had diastolic dysfunction when compared to 77% in the normal weight category.

Diastolic Dysfunction and Risk factor group:

The patients were divided into six risk factor groups. Highest percentage of diastolic dysfunction was observed in patients who had hypertension, diabetes mellitus as well as dyslipidemia.

There was no significant difference in the prevalence of diastolic dysfunction between patients who had only hypertension and those who had only diabetes.

There was not much statistically significant association between the risk factor groups and diastolic dysfunction.

Khalil S J et al. (2007) estimated that about 58% of the diabetic patients had diastolic dysfunction of which majority of them had Grade I diastolic dysfunction. Cosson et al. (2007) demonstrated that 69% of the diabetics have abnormalities in diastolic filling.

A Nigerian study SO Ikeh et al. (2006) reported the prevalence of diastolic dysfunction in hypertensive patients as high as 82.86% where as in normotensive controls it was 34.29%.

Verdecchia P et al. (1990) reported a prevalence of 46-48% of diastolic dysfunction in hypertensive patients in European population.

hs- CRP and Diastolic dysfunction:

High statistical significance (**P < 0.001****) was observed for the association between hs-CRP and diastolic dysfunction.

Out of the patients with diastolic function (n=62) 91% showed a definite positive association between their serum hs-CRP levels and degree of diastolic dysfunction.

Rajaram V et al (2011) in a study that included the assessment of diastolic dysfunction in African Americans with cardiovascular risk factors found out a significant association between diastolic dysfunction and hs-CRP levels.

Masugata et al. (2011) a Japanese study which assessed the association between hs-CRP levels and Doppler echocardiographic parameters of diastolic dysfunction in patients with cardiovascular risk factors also reported definite correlation.

Hence based on our study and recent studies as quoted we suggest that serum hs-CRP can be used as a marker for diastolic dysfunction in patient with cardiovascular risk factors.

CONCLUSION

According to our study conducted on 100 patients with cardiovascular risk factors without clinical evidence of heart failure and normal systolic function.

- Diastolic dysfunction is common in patients with cardiovascular risk factors such as hypertension, diabetes mellitus and dyslipidemia. Grade I diastolic dysfunction is more commonly encountered. Grade III and Grade IV diastolic dysfunction were not encountered. Hence echocardiographic evaluation is needed in all patients with cardiovascular risk factors.
- Increasing age in patients with cardiovascular risk factors is associated with increased prevalence of diastolic dysfunction. Especially above 50 years.
- Female sex has a marginally higher prevalence of diastolic dysfunction when compared to males.
- Obesity has a very strong correlation with diastolic dysfunction.
- More the number of cardiovascular risk factors in a patient more are the chances of developing diastolic dysfunction.
- hs- CRP levels have a significant association with diastolic dysfunction in patients with cardiovascular risk factors. This relationship is independent of all other risk factors.

- Therefore hs-CRP can be used as a marker for diastolic dysfunction in patients with cardiovascular risk factors, who are asymptomatic.
- Treatment strategies targeted at the underlying pathogenic mechanisms could potentially reverse the diastolic dysfunction and thereby reduce cardiovascular mortality.

ANNEXURE

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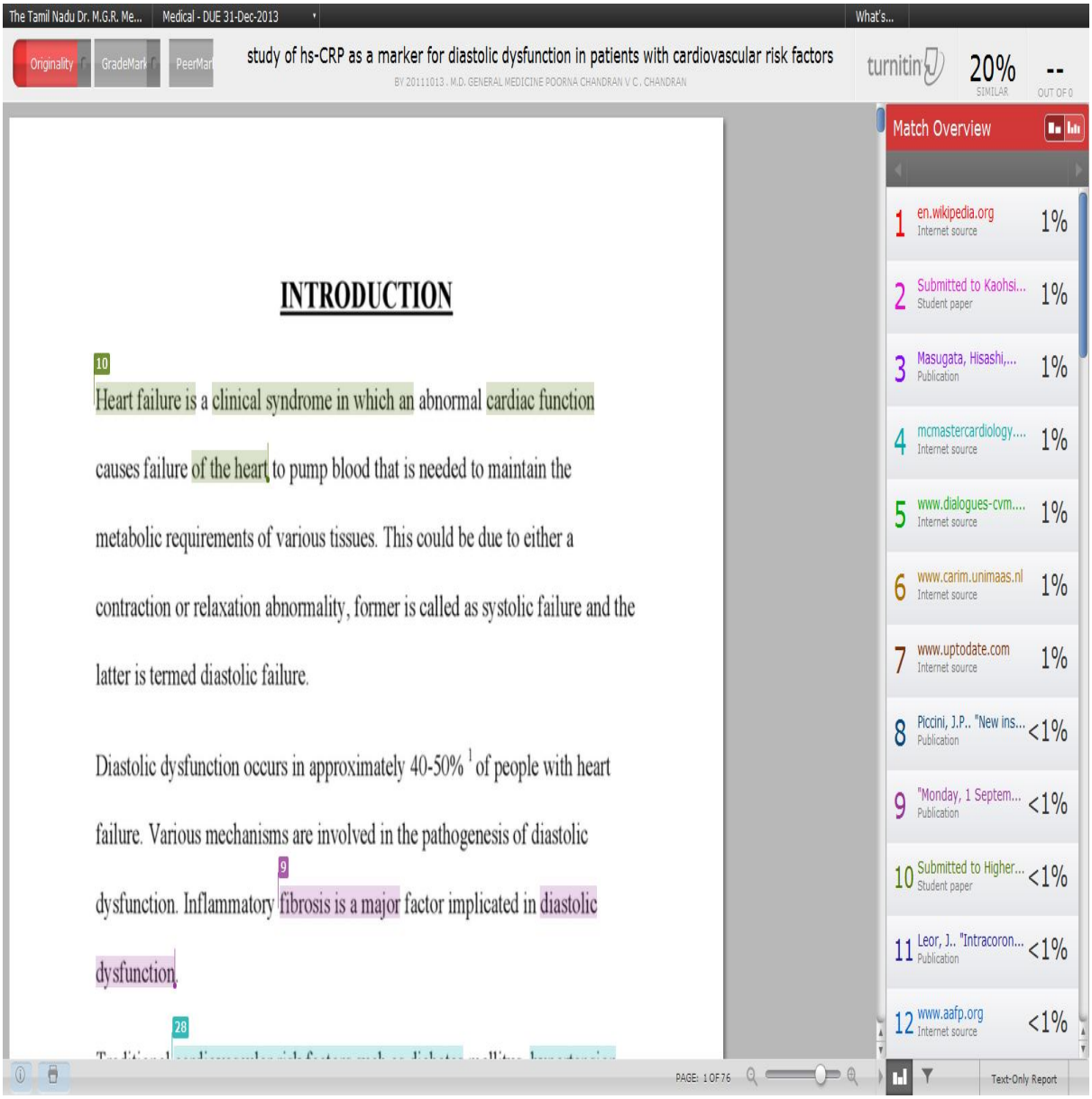
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INTRODUCTION
Heart failure is a clinical syndrome in which an abnormal cardiac function causes failure of the heart to pump blood that is needed to maintain the metabolic requirements of various tissues. This could be due to either a contraction or relaxation abnormality, former is called as systolic failure and the latter is termed diastolic failure.
Diastolic dysfunction occurs in approximately 40-50% [1] of people with heart failure. Various mechanisms are involved in the pathogenesis of diastolic dysfunction. Inflammatory fibrosis is a major factor implicated in diastolic dysfunction.
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fibrosis is a major factor implicated in diastolic dysfunction.
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cardiovascular risk factors such as diabetes mellitus, hypertension are
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pro-inflammatory states that could cause myocardial stiffening and result in diastolic dysfunction.
C - reactive protein (CRP) is an acute phase protein produced in the liver in response to inflammation in the body. It
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has been used to predict cardiovascular risk in the general population.
3
1 1% match (Internet from 08-Sep-2013)
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INTRODUCTION Heart failure is a clinical syndrome in which an abnormal cardiac function causes failure of the heart to pump blood that is needed to maintain the metabolic requirements of various tissues. This could be due to either a contraction or relaxation abnormality, former is called as systolic failure and the latter is termed diastolic failure. Diastolic dysfunction occurs in approximately 40-50% 1 of people with heart failure. Various mechanisms are involved in the pathogenesis of diastolic dysfunction. Inflammatory fibrosis is a major factor implicated in diastolic dysfunction. Traditional cardiovascular risk factors such as diabetes mellitus, hypertension are pro-inflammatory...

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

Telephone No : 044 25305301
Fax : 044 25363970
EC RegNo.ECR/270/Inst./TN/2013

CERTIFICATE OF APPROVAL

To
Dr.V.C.Poornachandran,
MD General medicine PG,
Madras Medical College, Chennai-3.

Dear V.C.Poornachandran,

The Institutional Ethics committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled "High Sensitivity C- Reactive Protein as a marker for Diastolic function in patient with Cardiovascular Risk Factors" No.15062013.

The following members of Ethics Committee were present in the meeting held on 11.06.2013 conducted at Madras Medical College, Chennai -3.

1. Dr.SivaKumar, MS FICS FAIS --- Chairperson
2. Prof. R. Nandhini MD -- Member Secretary
   Director, Instt. of Pharmacology ,MMC, Ch-3
3. Prof. Shyamraj MD -- Member
   Director i/c , Instt. of Biochemistry , MMC, Ch-3
4. Prof. P. Karkuzhali. MD -- Member
   Prof., Instt. of Pathology, MMC, Ch-3
5. Prof. A. Radhakrishnan MD -- Member
   Prof of Internal Medicine, MMC, Ch-3
6. Prof. S. Deivanayagam MS -- Member
   Prof of Surgery, MMC, Ch-3
7. Thiru. S. Govindsamy. BABL -- Lawyer
8. Tmt. Arnold Saulina MA MSW -- Social Scientist

We approve the proposal to be conducted in its presented form.

Sd/ Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

R.Nandhini
Member Secretary, Ethics Committee
24/6/13

PROFORMA

HIGH SENSITIVITY C-REACTIVE PROTEIN AS A MARKER FOR DIASTOLIC DYSFUNCTION IN PATIENTS WITH CARDIOVASCULAR RISK FACTORS

Name: Age: Sex:

Address: Occupation:

Symptoms:

- Dyspnea
- Orthopnea\PND
- Syncope\palpitation
- Chest pain
- Oliguria
- Abdominal distension
- Swelling of legs
- Puffiness of Face
- Fever

Past history:

- Diabetes mellitus
- Hypertension
- Dyslipidemia
- Coronary artery disease/CVA/RHD
- Other co morbid illnesses

Personal history: Smoking, Alcoholism

General examination:

Anthropometry: Height(in cm): Weight(in kg):

PULSE: **BLOOD PRESSURE:**

GENERAL EXAMINATION:

SYSTEMIC EXAMINATION:

CVS: RS:

ABDOMEN: CNS:

INVESTIGATIONS:

Hb: TC: DC: ESR:

Blood Glucose(Fasting) :

Blood Urea :

Serum Creatinine :

Total Cholesterol : HDL :

Triglycerides : LDL :

Hs-CRP :

ECG:

ECHO CARDIOGRAM:

PATIENT CONSENT FORM

Study Detail : "**HIGH SENSITIVITY C-REACTIVE PROTEIN AS A MARKER FOR DIASTOLIC DYSFUNCTION IN PATIENTS WITH CARDIOVASCULAR RISK FACTORS**"

Study Centre : Rajiv Gandhi Government General Hospital, Chennai.

Patient's Name :

Patient's Age :

Identification Number :

Patient may check (☑) these boxes

I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction. ☐

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ☐

I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ☐

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ☐

I hereby consent to participate in this study. ☐

I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological, biochemical, radiological tests. ☐

Signature/thumb impression	Signature of Investigator
Patient's Name and Address:	Study Investigator's Name:Dr.V.C.Poornachandran.

MASTER CHART

S.NO.	NAME	AGE	SEX	OP NO.	BMI	HT	DM	DL	GROUP	EF%	DD	hsCRP
1	Aysha beevi	52	F	2150	31.2	y	N	N	A	61	Gr-I	0.67
2	Rathnammal	51	F	5213	30.6	Y	Y	N	C	58	Gr-I	0.78
3	Dhanasekaran	60	M	4450	30.6	Y	N	N	A	62	Gr-I	0.59
4	Srinivasan	60	M	1886	32.9	Y	Y	N	C	57	Gr-II	1.67
5	Radhakrishnan	56	M	3573	31.5	Y	Y	N	C	61	Gr-II	1.97
6	Kuppusamy	60	M	2412	32.5	y	N	N	A	59	Gr-I	0.74
7	Marimuthu	50	M	1888	27.9	Y	Y	N	C	63	NIL	0.32
8	Murugan	30	M	3226	24.2	Y	N	N	A	64	NIL	0.19
9	Senthamarai	68	M	3539	32.7	Y	N	N	A	56	Gr-II	1.04
10	Meena	45	F	5588	29.8	Y	N	Y	D	58	Gr-I	0.64
11	Perumal	60	M	3478	28.4	Y	N	N	A	62	Gr-I	0.73
12	Subramani	57	M	1851	33.4	Y	N	N	A	63	Gr-I	0.81
13	Ramamurthy	70	M	1514	30.5	Y	N	N	A	58	Gr-II	1.62
14	Murugesan	58	M	2197	33.5	Y	Y	Y	G	56	Gr-II	2.25
15	MeharTaj	39	F	3696	23.4	Y	N	N	A	62	NIL	0.24
16	Anwar basha	70	M	4731	34.7	Y	Y	N	C	56	Gr-II	2.17
17	Munipandi	65	M	1311	28.4	Y	Y	N	C	59	Gr-II	1.97
18	Padma	52	F	5581	34.8	Y	Y	N	C	57	NIL	0.48
19	Munikrishnan	57	M	1594	36.2	Y	N	N	A	62	Gr-I	0.83
20	Aravalli	53	F	1571	32.5	Y	Y	N	C	54	NIL	0.25
21	Jagadesswari	55	F	1661	28.4	Y	N	N	A	58	Gr-I	0.73
22	Rani	57	F	1750	32.5	Y	N	N	A	61	Gr-I	0.61
23	Gangammal	58	F	2735	30.5	Y	N	N	A	54	Gr-I	0.58
24	Hussain beevi	60	F	2522	32.5	Y	N	N	A	56	Gr-II	1.37
25	Jothi	58	F	4697	33.5	Y	N	N	A	60	Gr-I	0.91
26	Baskar	58	M	2742	33.9	Y	Y	N	C	57	Gr-II	2.05
27	Mohanraj	56	M	4316	29.4	Y	N	N	A	62	NIL	0.34
28	Savitha	45	F	1873	27.4	Y	N	N	A	63	NIL	0.41
29	Kannagi	42	F	1691	26.4	Y	N	N	A	61	NIL	0.27
30	Selvakumari	60	F	1885	33.4	Y	Y	N	C	55	Gr-I	0.86
31	Paappammal	75	F	1420	29.4	Y	Y	N	C	59	Gr-I	0.92
32	Usha rani	45	F	1105	26.4	Y	N	N	A	64	NIL	0.14
33	Kanthammal	57	F	2584	28.4	Y	N	Y	D	62	Gr-I	0.54
34	Padmavathy	47	F	6472	32.5	N	Y	N	B	61	Gr-I	0.61
35	Thenmozhi	38	F	4066	24.6	N	Y	N	B	63	NIL	0.39
36	Gandhi	51	M	7381	34.5	Y	Y	N	C	64	NIL	0.31
37	Narayanan	53	M	1959	32.4	N	Y	N	B	66	Gr-I	0.76
38	Subramani	55	M	2971	31	Y	Y	N	C	58	NIL	0.18
39	Venkaiya	64	M	5788	29.4	Y	Y	N	C	56	Gr-I	0.74
40	Jayalakshmi	69	F	3578	35.4	N	Y	N	B	64	Gr-II	1.34
41	Pavunammal	65	F	3477	28.4	N	Y	N	B	61	Gr-II	0.96

S.NO.	NAME	AGE	SEX	OP NO.	BMI	HT	DM	DL	GROUP	EF%	DD	hsCRP
42	Malliga	58	F	1768	33.7	Y	y	N	C	58	Gr-I	0.63
43	Muthulaksmi	45	F	4129	34.8	N	Y	N	B	64	Gr-I	1.12
44	Viola mary	55	F	3659	28.4	N	Y	N	B	65	Gr-I	0.83
45	Venkatesh	40	M	1223	27.4	N	Y	N	B	68	Gr-I	0.76
46	Arumugam	55	M	4449	33.4	Y	Y	N	C	62	Gr-I	0.84
47	Kannadas	48	M	4456	26.7	Y	Y	N	C	64	NIL	0.74
48	Parimala	66	F	3560	36.4	Y	Y	Y	G	61	Gr-II	2.54
49	Sarada	65	F	2262	35.7	N	Y	N	B	66	Gr-I	0.71
50	Selvaraj	52	M	3409	33.7	N	Y	N	B	67	Gr-II	1.31
51	Raji	42	M	4511	24.5	N	Y	N	B	65	NIL	0.27
52	Manickam	45	M	4803	26.4	N	Y	N	B	66	Gr-I	0.61
53	Balan	61	M	5174	34.5	Y	Y	N	C	61	NIL	0.17
54	Manonmani	75	F	2165	32.7	Y	Y	Y	G	58	Gr-II	2.55
55	Kathiravan	40	M	5261	28.4	N	Y	N	B	67	NIL	0.48
56	Vasanthan	60	M	2524	35.7	Y	Y	N	C	64	Gr-II	1.65
57	Rajendran	49	M	4382	29.4	y	y	N	C	60	Gr-I	1.24
58	Ansari Ahmed	65	M	3068	35.8	Y	Y	Y	G	61	Gr-II	1.85
59	Chandra	62	F	7467	34.7	Y	N	Y	D	62	Gr-II	1.62
60	Ganesan	41	M	2910	28.2	N	Y	N	B	63	NIL	0.17
61	Tamilselvi	44	F	1769	32	Y	N	Y	D	64	NIL	0.48
62	Amudha	38	F	1356	24.2	N	Y	N	B	62	NIL	0.31
63	Ramesh	36	M	5014	23.8	N	Y	N	B	66	NIL	0.21
64	Kamala	61	F	8024	33.6	Y	Y	Y	G	59	Gr-I	2.14
65	Saroja	49	F	3548	31.2	N	Y	Y	E	60	NIL	0.36
66	Ayyappan	39	M	1982	26.2	Y	N	Y	D	68	NIL	0.21
67	Dhandapani	55	M	4687	30.5	Y	Y	Y	G	57	Gr-I	1.95
68	Chandrasekar	41	M	3121	27.6	N	Y	Y	E	63	NIL	0.24
69	Ganga	45	F	8420	29.4	N	Y	Y	E	59	NIL	0.41
70	leelavathy	42	F	4306	31.4	Y	N	Y	D	60	NIL	0.39
71	Arasu	52	M	1274	32.7	Y	Y	Y	G	58	Gr-I	0.85
72	Rajalaksmi	59	F	2145	33.7	N	Y	Y	E	56	Gr-II	1.24
73	Krishnaveni	56	F	3015	30.6	Y	Y	N	C	59	Gr-I	0.82
74	Ravi kumar	50	M	2187	29.4	N	Y	Y	E	61	NIL	0.26
75	Jothimani	62	M	5014	33.7	Y	Y	Y	G	57	Gr-II	1.76
76	kalaiselvi	33	F	1031	26.7	N	Y	Y	E	64	NIL	0.31
77	Indra	39	F	2597	27.3	Y	N	Y	D	66	NIL	0.41
78	Shamshad	48	M	8245	29.4	Y	Y	N	C	61	NIL	0.24
79	soundarajan	45	M	6017	28.2	N	Y	N	B	62	Gr-I	0.72
80	Kuppan	42	M	3587	27.3	Y	N	Y	D	65	NIL	0.28
81	Ahmed basha	50	M	1305	32.7	Y	Y	Y	G	59	NIL	0.47
82	lewis	47	M	5124	26.8	N	Y	Y	E	63	NIL	0.41
83	Akbar Ali	55	M	5385	32.5	Y	Y	Y	G	58	Gr-I	1.25
84	Dhanalakshmi	50	F	6501	31.3	N	Y	Y	E	59	Gr-I	0.95
85	Munusamy	51	M	8055	30.8	Y	Y	Y	G	56	NIL	0.26

S.NO.	NAME	AGE	SEX	OP NO.	BMI	HT	DM	DL	GROUP	EF%	DD	hsCRP
86	Anbu	45	M	4782	29.4	Y	N	Y	D	64	Gr-I	0.69
87	Jaya kumar	58	M	6612	32.4	Y	Y	Y	G	56	Gr-II	2.36
88	Lakshmi devi	52	F	1236	30.5	N	Y	Y	E	58	Gr-I	0.81
89	Kannaiah	58	M	3025	31.6	Y	Y	Y	G	56	Gr-I	1.68
90	Mohanraj	42	M	1789	24.7	Y	N	N	A	62	NIL	0.39
91	Jamuna	50	F	1857	29.3	Y	N	Y	D	59	Gr-I	0.71
92	Siva kumar	40	M	6125	28.6	N	Y	N	B	66	Gr-I	0.83
93	Baskar	49	M	5241	32.8	N	Y	Y	E	61	NIL	0.36
94	Shanthi kala	64	F	4589	34.2	Y	Y	Y	G	56	Gr-II	2.23
95	Rose mary	45	F	7541	29.5	N	Y	Y	E	60	NIL	0.23
96	Muthpandi	52	M	3698	31.6	N	Y	Y	E	59	Gr-I	0.95
97	Praskash	36	M	4658	28.5	N	Y	N	B	68	NIL	0.19
98	Lalitha	46	F	1087	29.4	N	Y	Y	E	61	NIL	0.26
99	Muthusamy	54	M	5713	27.4	N	Y	Y	E	59	Gr-I	0.79
100	Balaji	48	M	6278	26.3	N	Y	N	B	60	Gr-I	0.73

KEY TO MASTER CHART

BMI- BODY MASS INDEX

HT- HYPERTENSION

DM- DIABETES MELLITUS

DL- DYSLIPIDEMIA

EF-EJECTION FRACTION

DD- DIASTOLIC DYSFUNCTION